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CONSTITUTIONAL TRUE SEXUAL PRECOCITY

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IDIOPATHIC true sexual precocity has appeared with increasing frequency in recent years in males as well as in females. Indeed, the most common cause of precocious androgen activity as indicated by Seckel[1] in his review of the literature prior to 1946 is pituitary gonadotrophin stimulation, without detectable cause, entirely consistent with the occurrence of a normal puberty but at an abnormally early age. The familial occurrence of a similar syndrome has been noted and lends support to the concept that the isolated case is also a constitutional disorder (constitutional meaning an intrinsic characteristic of the organism, i.e., not acquired by the individual). However, demonstration of precocious procreative ability with spermatogenesis has not been reported in familial cases, though it has been detected in isolated cases in which the constitutional basis of the disorder remains in doubt. It is the purpose of this report to present a family exhibiting precocious androgen activity in many of its male members, in which the demonstration of precocious spermatogenesis supplies the missing link between obviously constitutional, familial, precocious androgen activity and isolated, idiopathic, true sexual precocity, thereby proving the occurrence of constitutional true sexual precocity.

From the Pediatric and Infectious Disease Section, William Beaumont Army Hospital, Fort Bliss, Texas.

CASE REPORT

1. C. C., a 4-year-old white male, was admitted to William Beaumont Army Hospital for study because of precocious physical development of two years' duration. He had been entirely normal until 20 months of age when a sudden increase in growth was noted. He walked at 11 months, and never demonstrated any mental or neurological abnormalities. At 2 years he weighed 40 pounds and was 37 inches tall. Pubic hair and rapid enlargement of both penis and testicles were first noted at this time. He exhibited particularly firm, strong muscles and was able to outperform his playmates in competitive sports and feats of strength. Rapid genital and somatic growth continued until the time of admission. No advanced sexual interests were noted at any time. The patient adapted well to the play activities of his contemporaries.

Physical examination at the time of admission revealed a boy appearing to be approximately 7 or 8 years of age but exhibiting the muscular development of a young adult. No neurological abnormalities were detected. The optic fundi were normal and no abnormalities of the visual fields were detected. No abnormal masses were palpated in the abdomen. Skeletal musculature was unusually well developed, firm, and strong. The penis was 11 cm. in length and 8.5 cm. in circumference. The scrotum hung below the end of the penis and contained approximately adult-sized, 3.5 cm. long, symmetrical testicles. No axillary or facial hair was noted but a few comedones and acne were apparent on the nose and forehead. The voice was

husky. The blood pressure was approximately 95/65 on repeated occasions.

No evidence of adrenal cortical hyperactivity was detected. The white blood count was 8,000, the total eosinophil count 184 per cubic millimeter, the serum cholesterol 142 mg. per 100 c.c., the serum sodium 155 meq. per liter, the serum potassium 4.6 meq. per liter, the serum chlorides 99 meq. per liter,

Fig. 1.—C. C. at age 4 years, demonstrating precocious androgen effect upon the development of the musculoskeletal system, and secondary sex characteristics.

and the total protein 6.9 Gm. per 100 c.c. with 5.3 Gm. albumin and 1.6 Gm. globulin. Urinalysis was entirely normal. Glucose tolerance test showed no abnormalities. Roentenographic studies revealed no abnormalities of the skull or sella turcica, but an increase in bone age to approximately 10 years. Intravenous pyelography revealed normal renal pelves and ureters with no evidence of extrinsic compression.

Evaluation of the central nervous system by electroencephalography revealed a normal record of medium voltage and 4 to 6 per second rate without evidence of focal or paroxysmal discharges. Pneumoencephalography revealed no dilatation, distortion, or other abnormality of the ventricular system or of the basal cisterns which were well visualized. Developmental evaluation revealed motor, speech, personal-social, and adaptive behavior at the 48- to 54-month level.

Prostatic examination by Lt. Col. R. C. Rauscher showed a definite prostate gland usually not detectable at this age. There was considerable secretion following massage of the gland (including the seminal vesicle areas). The secretion appeared essentially normal for an adult with considerable corpora amylacea and an average of 3 to 5 sperm per high-power field. Approximately one of 15 to 20 sperms was motile on immediate examination. A considerable number appeared to be defective having two heads or two tails. Some had shortened tails and in some the heads were abnormal in size and shape.

Urinary hormone excretion studies appear in Table I.

2. E. C., a 28-year-old white male, the father of C. C., was apparently entirely normal until 22 months of age when he had a moderately severe attack of typhoid fever. Two months thereafter rapid muscular and skeletal growth became apparent for the first time. Simultaneously, pubic hair appeared and the penis and testicles rapidly enlarged. He was hospitalized for study at this time (1923) and because of the presence of the above signs and the absence of apparent local disease of the adrenal cortex or gonads, a diagnosis of possible "pineal gland tumor with physical precocity" was entertained. He did well in school, advanced normally, made excellent grades, and apparently had no social difficulties despite his unusual size and muscular development during this pe-

riod. He was rehospitalized for study at age 13, at which time he exhibited the physical and mental appearance of an adult 18 to 21 years of age. His beard was well developed as was the pubic, axillary, and abdominal hair. Genitalia appeared consistent with those of a 20-year-old male. Neurological examination as well as the remainder of the physical examination was entirely normal.

United States Air Force, still 64 inches in height, weighs 135 pounds, and is entirely normal in appearance. There is no evidence of any neurological defect or any endocrine disorder. He had always adapted well to the activities of his contemporaries and demonstrated no psychologic defects at the time of examination. Urine endocrine excretions are presented in Table I and are normal for the patient's age.

TABLE I. URINARY ENDOCRINE EXCRETION IN C. C. AND E. C.

		C. C.—4 YR.	E. C.—28 YR.
17-ketosteroids— mg. per 24 hours	Total	7.77	4.32
	Alpha	4.62	1.62
	Beta	3.15	2.70
11-Oxycorticosteroids— mg. per 24 hours	Total	--	1.4
Gonadotrophins international mouse units	Total	Less than 50	--

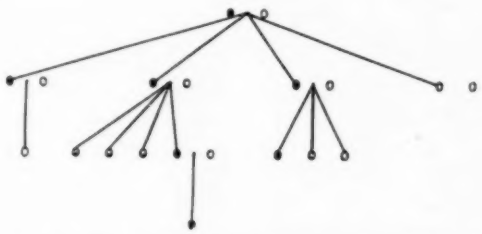

Fig. 2.—Family C., showing the relationship of affected males ●, unaffected males ⊖, and females ○, in the affected family units only.

Evaluation of his adrenal cortical activity revealed a blood pressure of 130/78, normal urine, and a normal glucose tolerance test. Radiological examination of the skull revealed no abnormalities of the sella turcica, no signs of increased intracranial pressure, and no intracranial calcifications. The basal metabolic rate was minus 10 and minus 4 per cent. He was 64 inches in height and 131½ pounds in weight.

Growth ceased at approximately 10 years. He remained well developed, stronger than average, and, though relatively short in stature by comparison with his contemporaries after age 12, his genital precocity gradually blended into the adolescent normal. At present, aged 28 years, he is a captain in the

3. Other members of the family.

Though unavailable for examination, five other members of this family have definitely exhibited sexual precocity, the great-grandfather and grandfather of C. C., two of the grandfather's three brothers, and the son of one of these brothers (see Fig. 2). This trait is apparent only in the direct descendants of affected males and presumably is only transmitted by them. This is obviously a heterozygous defect and several male descendants of affected individuals have not demonstrated the trait. The defect apparently does not affect females. Sexual precocity appeared prior to the age of 5 years in each of the affected members and pursued essentially the same course as in the two described individuals. Ap-

parently, the only residual effect has been a slight reduction in stature in each.

DISCUSSION

A large proportion of the cases of precocious androgen activity in males has been associated with increased adrenal cortical activity as hyperplasia or carcinoma. Rarely has this syndrome been associated with autonomous gonadal hyperactivity such as an interstitial (Leydig) cell tumor of the testis (eight reported cases).[1, 2] True sexual precocity with the early appearance of androgen effects and the ability to procreate has been commonly noted to produce this syndrome in males and even more frequently is associated with precocious estrogen activity in females.[3] A chorioepithelioma or similar embryonal neoplasm may rarely produce true sexual precocity, and is distinguished by the tremendous outpouring of urinary gonadotrophin as detected by the Aschheim-Zondek test.[4] Approximately one-third of the cases of true sexual precocity in males is associated with clinically apparent organic disease of the central nervous system with concomitant stimulation of the gonadotrophin output of the anterior pituitary.[1] A wide variety of pathologic processes has been associated with this syndrome, including encephalitis (viral, bacterial, and protozoal), tuberous sclerosis, congenital anomalies, hydrocephalus,[5] and several neoplasias,[6] all of which seem to produce a common effect on the vascular and/or nervous connections between the hypothalmus and the anterior pituitary as they course along the wall of the third ventricle (fifty-two reported cases).[1, 5, 6, 7, 8] An additional rare cause of true sexual precocity is the Albright syndrome (polyostotic fibrous dysplasia) of which four cases have been reported in males.[9, 10] The remaining group of patients with true sexual precocity demonstrates no organic cause for the syndrome, but appears to manifest normal procreative and androgenic activity at an early age due to precocious gonadotrophic stimulation from an apparently normal anterior pituitary.

Patients presenting this latter syndrome of idiopathic true sexual precocity are characterized by the appearance, usually before the age of 5 years, of rapid increase in skeletal and muscular growth, enlargement of the penis, pubic hair, deepening of the voice, and, in distinction from pseudosexual precocity, enlargement of the testicles with the onset of spermatogenesis. At least 101 such isolated cases have been reported or abstracted in the American literature.[1, 11, 12, 13, 14, 15, 16, 17, 18] This diagnosis has been made chiefly by the exclusion of other possible etiological factors occasionally aided by the discovery of urinary gonadotrophins (not normally present until after age 11 years[12]), or the demonstration of spermatogenesis by testicular biopsy.[16, 17] The diagnosis of many of these isolated cases has not been adequately proved by the satisfactory exclusion of organic disease, particularly of the central nervous system. It has been suggested that all cases of this type, if adequately studied, would demonstrate some organic intracranial disease which would account for the apparent stimulation of the anterior pituitary.[19] However, although no single isolated case has been reported to have been studied by testicular biopsy (or other means) to demonstrate spermatogenesis, by urinary endocrine studies to demonstrate gonadotrophin excretion in the pubertal range, and by neurological examina-

tion including pneumoencephalograms to rule out the presence of third ventricular dilatation or distortion, several cases have been evaluated by some combination of these three essential determinations and many cases have been followed for sufficiently long periods of time to strongly suggest that no organic abnormality was present. If urinary gonadotrophins are present, spermatogenesis may be assumed, but spermatogenesis may be consequent to the stimulation of the gonadotrophin of a chorioepithelioma (thus quantitative urinary gonadotrophin studies are essential to the diagnosis of idiopathic true sexual precocity), or the effect of an organic central nervous system lesion on the anterior pituitary (thus thorough evaluation of the third ventricular area, difficult to assess without a pneumoencephalogram, is essential to the diagnosis of idiopathic true sexual precocity). If urinary gonadotrophins are not detected (and their absence in readily detectable amounts is consistent with idiopathic true sexual precocity), then the demonstration of spermatogenesis is essential to this diagnosis as increased androgen secretion alone, from the adrenal cortex, the testes, or an embryonal neoplasm may account for all the superficial symptomatology.

In contrast to the somewhat uncertain status of the diagnosis of precocious androgen activity in the isolated case without detectable organic disease, its appearance as a familial defect, unassociated with concomitant organic disease and resulting in entirely normal adults except for slightly decreased stature due to early epiphyseal closure, demonstrates the at least occasionally constitutional nature of the condition. Indeed, its occurrence in this obviously hereditarily determined, relatively benign form suggests the possibility that the isolated cases of apparent true sexual precocity without detectable organic disease are also manifestations of a constitutional trait, possibly hereditarily determined. Five reports concerning the familial occurrence of apparent true sexual precocity in males have appeared in the literature and Dr. A. W. Jacobsen[20] is studying an additional family group in which a large number of males has demonstrated true sexual precocity. Stone[21] reported the appearance of this syndrome in a father and his son in 1852, Orel,[22] in two brothers in 1928, Rush and associates,[23] in a father, two sons, and at least four other relatives in 1937, and Sigrist,[24] in two brothers in 1940. Engstrom and Munson in 1951[25] reported the occurrence of probable true sexual precocity in a father and two sons and particularly noted the lack of any acceleration in the appearance of axillary and facial hair, teeth, 17-ketosteroid excretion, and intellectual capacity.

The presence of true sexual precocity has been assumed rather than proved in the reported familial cases. The low level of 17-ketosteroid excretion detected by Engstrom and Munson in their cases tends to deny the presence of adrenal cortical hyperactivity. The only gonadotrophin excretion studies in these familial cases are reported by the same authors who did not find a detectable urinary level. Spermatogenesis was not detected in the cases of Engstrom and Munson or in any other reported familial cases. No demonstrable central nervous system defect was detected by pneumoencephalogram in the several reported cases in

which this examination was attempted. The additional lack of other neurological abnormalities and the benign outcome of every case seem to contraindicate the presence of an organic lesion of the brain. Thus, the diagnosis of a hereditarily determined, constitutional defect which results in increased androgen activity has been determined but only by exclusion has it been demonstrated that this syndrome represents true sexual precocity. However, the determination of spermatogenesis with only slightly increased urinary gonadotrophin excretion, inconsistent with the presence of a secreting embryonal cell tumor, and the absence of a lesion of the central nervous system detectable by pneumoencephalogram (or other means) in the 4-year-old boy reported herein, a member of a family demonstrating familial androgenic precocity, proves directly that true sexual precocity of a constitutional nature occurs and that it may be hereditarily determined.

The cases reported illustrate three important aspects of idiopathic true sexual precocity. First, the definitive diagnosis of this syndrome in the male is simple. Although the detection of spermatogenesis by the examination of the prostatic fluid is usually unsuccessful even in the normal adult, it may be successful and thus should be attempted. C. C. is the first reported patient with sexual precocity in whom spermatogenesis was detected by examination of the prostatic fluid. If this technique is unsuccessful, the accessibility of the testis permits the use of testicular biopsy which is apparently without significant danger.[17] Palpable enlargement of the testicles suggests the presence of true precocity, while the determination of pubertal urinary gonadotrophin excretion corroborates this suggestion and indicates the probability of spermatogenesis. A normal or only slightly elevated gonadotrophin excretion denies the rare presence of a gonadotrophin-secreting embryonal tumor such as a chorioepithelioma which might account for true precocity. The combined use of electro- and pneumoencephalography and clinical neurological examination effectively rules out the possible presence of some hypothalamic abnormality which might cause early pituitary stimulation. Second, the simultaneous use of these examining techniques proves the presence of idiopathic true sexual precocity and its appearance as a familial defect in the reported cases proves its constitutional nature. The known prolonged and benign course in E. C. without concomitant neurological disease demonstrates that this defect is probably a functional derangement of the normal mechanism (probably within the hypothalmus) which initiates pituitary gonadotrophin secretion at the time of puberty, rather than an organic maldevelopment of the central nervous system. The possibility that the isolated cases of idiopathic true sexual precocity are also due to an hereditary, possibly recessive, defect is suggested. Third, these cases demonstrate the good prognosis of this condition. With a minimum of constructive psychotherapeutic control, E. C. progressed through an apparently normal early life. Only a slightly smaller stature than average has resulted. It is important to emphasize that though procreative ability was probably present prior to 4 years of age in each case, psychologic development was not unusually rapid and each affected individual progressed through an apparently

normal "childhood" period, biologic capabilities to the contrary. None is known to have demonstrated any unusual interest in sexual matters at an early age, but, on the contrary, participated in the usual activities of his contemporaries.

SUMMARY

The occurrence of constitutional true sexual precocity in at least seven male members of a single family is presented.

The author is indebted to Lt. Col. Robert Rauscher, William Beaumont Army Hospital, for his urological examination of the patient C. C. The assistance of Lt. Col. Robert Cavenaugh and the Laboratory Service, William Beaumont Army Hospital, in the accumulation of data and preparation of the figures is gratefully acknowledged. The author is grateful to the Medical Center, University of Kansas, for much of the data on the patient E. C.

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MUCOLYTIC ENZYME SYSTEMS

XVIII. Nonspecific Hyaluronidase Inhibitor Concentrations in the Blood Serum of Siblings and Parents of Children With Rheumatic Fever

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GENETIC susceptibility of the host to rheumatic fever appears to be an important factor in the acquisition of this disease.[1] An intriguing possibility exists that there is at least, in part, a biochemical basis for the difference between rheumatic susceptibles and nonsusceptibles. It has been shown that rheumatic fever patients appear to respond to streptococcal infections with a greater production of antibodies to the streptococcal antigens.[2, 3, 4] These observations of the antibody response, however, have not been extended to other members of the family.

In earlier communications Good and Glick[5] and Dorfman[6] described an elevation of the serum nonspecific hyaluronidase inhibitor in the early phases of rheumatic fever with subnormal inhibitor levels occurring in the period of convalescence from this disease. It was the experience of Good and Glick as well as our experience that patients with convalescent and inactive rheumatic fever *regularly* had subnormal serum hyaluronidase inhibitor values. Good and Glick were unable to conclude, however, whether the consistently lower values noted had a special significance, but they stated, "It is certain from extensive clinical studies that patients such as those studied in this group represent a population more susceptible to the ravages of rheumatic disease than groups of normal children. If hyaluronidase activity plays a role in the pathogenesis of rheumatic fever, the differences in serum inhibitor concentrations might have considerable bearing on the relative susceptibility of various individuals to rheumatic disease."

No studies have been performed to date to demonstrate whether individuals who develop rheumatic disease have low hyaluronidase inhibitor levels before the onset of the disease. The possibility exists, however, that such a condition might occur. If susceptibility to rheumatic fever is in part due to genetic factors and susceptible individuals have low hyaluronidase inhibitor values, these low values might also be found in the sera from a significant percentage of siblings and parents of the rheumatic fever subjects.

The purpose of this communication is to report the results of studies on the concentration of the nonspecific hyaluronidase inhibitor in the sera of sixty-four parents and sixty-seven siblings of rheumatic fever subjects and to compare the results with those from seventy-one normal individuals from families in which no known cases of rheumatic disease had occurred.

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MATERIALS AND METHODS OF STUDY

The viscosimetric method previously employed[7, 8] was used for the determination of the nonspecific hyaluronidase inhibitor in the blood serum. The concentration of the inhibitor was expressed in terms of per cent inhibition of the activity of a standard bovine testicular hyaluronidase preparation acting on a standardized hyaluronic acid substrate prepared from human umbilical cords.[9]

All specimens of blood were obtained by venipuncture, allowed to clot for one hour and then centrifuged for fifteen to twenty minutes. The serum was poured off and stored in the deep frozen state until used. Specimens from the normal control individuals and from members of the families of rheumatic fever subjects were collected and studied simultaneously to obviate possible variabilities in storage as well as in measurement. In all instances blood samples were collected from individuals without infectious disease. Blood was obtained only from those parents and siblings of rheumatic fever subjects who *definitely* had rheumatic heart disease and whose illness we had observed.

RESULTS

The results obtained through these tests on the sera of control (normal) individuals, and on the parents and siblings of rheumatic fever patients, are shown in Table I. The means for the three groups are listed, as well as the standard deviations and the standard errors of the means. There were moderate differences between the means of the controls and the other two groups, but these differences were not statistically significant. Using the equation

$$k = \frac{\bar{x} - \bar{y}}{\sqrt{SE\,x^2 + SE\,\bar{y}^2}}$$

the k value in each comparison (e.g., control: parent; control: sibling) was below 2, the critical value.

In reviewing the data, it is obvious that the distributions differ considerably; this is indicated by an excess of low values in the sibling and parent groups. The tendency toward bimodality in these groups can be clearly seen in the frequency (Table II) and in the distribution curve in Fig. 1.

The fourfold table method was used for testing the significance of these differences in distribution. The values for parents and siblings were combined, and a comparison was made between the number of values below 15 (chosen in order that all categories would include at least five individuals) in this group as compared to the con-

TABLE I

	NO.	MEAN PER CENT INHIBITION OF HYALURONIDASE	STANDARD DEVIATION	STANDARD ERROR OF MEAN
Controls	71	16.8	±3.9	±0.46
Siblings	67	15.6	±4.0	±0.49
Parents	64	15.9	±3.9	±0.49

TABLE II

	NO.	PER CENT INHIBITION OF HYALURONIDASE																			--	
		8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	--	42
Controls	71	0	0	1	0	1	0	5	22	19	3	7	4	3	2	1	0	1	1		1
Siblings	67	0	2	0	6	6	5	5	11	7	8	4	5	1	2	1	0	3	1		0
Parents	64	2	2	0	8	3	0	4	5	9	11	5	7	1	3	1	1	1	1		0

TABLE III

	RANGE OF PER CENT INHIBITION		TOTAL NO.
	0-14	15-42	
No. controls	7(a)	64(b)	71(e)
No. parents and siblings	43(c)	88(d)	131(f)
Total	50(g)	152(h)	202(n)

$$X^2 = \frac{N\ (ad - bc)^2}{efgh} = \frac{202\ (7 \times 88 - 64 \times 43)^2}{71 \times 131 \times 50 \times 152} = 13.0$$

Degrees of freedom = 1
Probability is less than 0.001

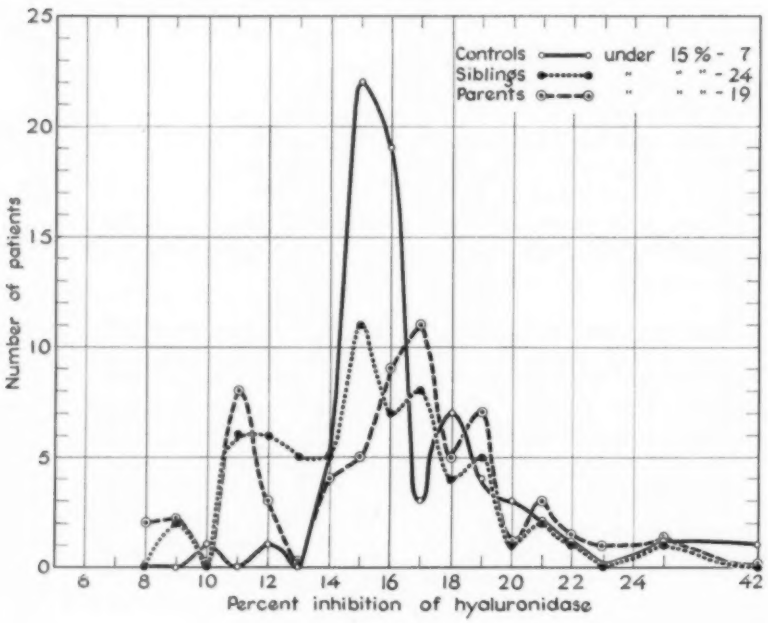

Fig. 1.

trol group. Table III shows the results of this analysis.

The probability according to this method is less than 0.001. This indicates that the two groups are different with respect to the occurrence of low values for the hyaluronidase inhibitor.

DISCUSSION

Although the number of parents and siblings of rheumatic fever subjects studied in this series is small, the evidence would suggest that a significant number of these individuals has abnormally low nonspecific hyaluronidase inhibitor values when compared with the normal controls. There is no evidence as yet, however, to permit one to implicate low hyaluronidase inhibitor values with rheumatic fever susceptibility but such a thesis seems entirely possible and the present data tend to support it. The following two observations are in accord with this contention:

1. Sibling M. N., 11-year-old female, had a hyaluronidase inhibition of nine per cent on June 3, 1951. At this time she was well and had had no history of rheumatic fever. Two months later she developed fever, polyarthritis, and a diagnosis of acute rheumatic fever was made. In spite of salicylates and bed rest she gradually became worse and expired fifteen days later. Terminally this patient also had evidence of nephritis.

2. Sibling R. C., an identical twin of a patient with rheumatic disease, had a hyaluronidase inhibitor value of 12 per cent on July 17, 1950. This sibling likewise had no history of rheumatic disease previous to the determination of the test.

The possibility is recognized that some of the parents and siblings of the rheumatic patients may have had undetected rheumatic disease themselves at one time, and that in any case their greater exposure to the disease may also be a factor in the present consideration. These possibilities emphasize the need for continued study of the question of a possible relationship between the hyaluronidase inhibitor and susceptibility to rheumatic fever.

It is not the purpose of this communication to elaborate on the potential value in ascertaining biochemical differences between rheumatic fever susceptibles and the normal individual. It is obvious, however, that any differences between the two groups could be used to study the many facets of the disease such as its epidemiology, prevention, and treatment.

SUMMARY

The blood sera from sixty-four parents and sixty-seven siblings of rheumatic fever subjects and seventy-one normal individuals were analyzed for their concentration of nonspecific hyaluronidase inhibitor. Forty-three parents and siblings (33 per cent) had values below 15 per cent inhibition of hyaluronidase, whereas only seven normal individuals (10 per cent) had such low values. This difference was found to be statistically significant.

The authors are indebted to Miss Mary J. Ochs for her technical assistance in carrying out the analyses.

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ELECTROENCEPHALOGRAPHIC DIAGNOSIS OF CEREBRAL PATHOLOGY IN INFANTS DURING SLEEP

I. Rationale, Technique, and the Characteristics of Normal Sleep in Infants*

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ALTHOUGH electroencephalography is now an established clinical tool for the diagnosis of cerebral pathology in adults and older children, very little progress has been made toward establishing the technique as a reliable aid to diagnosis in infants and very young children. This is an unfortunate circumstance since it seems likely that electroencephalography, being a nontraumatic technique and a relatively pleasant procedure for the patient, should have its greatest application in the very young. Furthermore the demand in this group is great, for the infant brain is by its very nature particularly susceptible to injury and, as it well known, the incidence of convulsive disorders is far greater during the first three years of life than at any other age.[1, 2] In addition, the often bizarre symptoms of the various encephalopathies and epileptoid states in infants[3] are notoriously difficult to evaluate and often pass unrecognized as manifestations of cerebral pathology until time or further progression of symptoms reveals their true nature. As will be shown in the next section of this paper, the electroencephalogram in many such cases may yield the only objective information obtainable.

The chief reason why infant electroencephalography has not been established on a sound clinical basis is that a suitable method of obtaining diagnostically reliable tracings in very young patients has not hitherto been evolved. The failure to develop an adequate technique has in turn resulted in a lack of adequate criteria for interpretation.

Obviously, the major problem of routine clinical electroencephalography in infants is that of obtaining a tracing sufficiently free of artifact that it can be read with the confidence that all activity is either of cerebral origin or clearly distinguishable from it. In children less than 3 years of age, the application of the electrodes is in itself a very difficult undertaking, but even if the technician succeeds in applying the electrodes, the problem of maintaining them in position and of keeping the infant relatively immobile remains. Restraint is unsatisfactory because it usually succeeds only in causing increased struggling and further emotional upset, factors which are hardly conducive to adequate electrical recording.

Barnes and co-workers[4, 5, 6, 7, 8] and Laplane and associates[9, 10] have at-

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tempted to circumvent the difficulties presented by the struggling infant by the use of deep barbiturate narcosis or light anesthesia. The results reported by these workers were not impressive inasmuch as no systematic attempt was made to establish definitive criteria for the interpretation of the tracings so obtained, resulting in the one instance in misinterpretation of normal sleep patterns as being epileptiform in nature. As will be shown in the next section of this paper, narcosis and deep sleep are not productive of abnormal activity and the sudden induction of sleep by anesthetics is in most cases of little, if any, value in obtaining diagnostic information.

METHODS

The recordings were made with the patient lying on a bed in a shielded, dimly lit or darkened semisoundproof room. The electroencephalograph employed was a six-channel Offner Type D dynograph, this instrument being particularly suitable to sleep recording in children because the nonblocking nature of the amplifiers, and the large excursion permitted by the dynograph, make it possible to obtain clearly delineated tracings without recourse to excessive attenuation of the interparoxysmal activity in the presence of the extremely high voltage electrical discharges which are recorded during sleep.

Nembutal was used throughout this study because it proved the most generally satisfactory for this purpose of all drugs tested. It is readily available in suppository form in four sizes ranging from ½ to 3 grains. It is our belief that the use of suppositories is less likely to produce the high irritability and excitement which barbiturates administered by "faster" routes are likely to produce in infants.* The onset of sleep is usually gradual, and although the sleep produced is generally profound, the patients are not unusually difficult to arouse at the end of the recording period and there are no ill effects such as excessive drowsiness or irritability. In normal infants, the amount of barbiturate-induced fast activity is negligible. On the other hand, with increased dosage it may be sufficient in the early stages of sleep to indicate depressed areas as in subdural hematoma, porencephaly, etc. Repeated studies in the same child have shown that Nembutal-induced sleep with the dosages employed by us does not differ from that which is spontaneous.

One-grain Nembutal suppositories were used in all children between the ages of 5 and 36 months; ½ grain suppositories were used in all infants younger than 5 months; ⅛ to ¼ grain Nembutal elixir was sometimes added if the child did not show signs of going to sleep within a reasonable period of time. Early in this study we learned that if a child responds to a small dose of a barbiturate by becoming irritable and restless, giving more aggravates rather than helps the situation. Furthermore, it has been our experience that if much larger doses are given to very young patients epileptiform activity is less likely to appear and the record will often be obscured by excessive fast activity of high amplitude.

Using the dosage recommended, the present percentage of sleep in our young patients is approximately 94

*In addition, the administration of barbiturates by mouth is usually difficult in infants and often produces gagging or vomiting, especially following feeding.

per cent. This has risen to its present level with continued experience from about 68 per cent when the study was first started.

Where possible the suppository is inserted fifteen to twenty minutes prior to arrival at the laboratory. The electrodes are generally applied while the patient is being held in the mother's or an assistant's arms. In many instances the electrodes were applied while the child slept.

Electrodes.—Ten electrodes (frontal, central, occipital, temporal, and two ears, or in some cases a Wilson-type* reference electrode) and a mastoid ground are applied routinely. A "dry" bentonite paste is used as an electrode jelly, only enough being applied to fill the cup of the electrode. A small area where the electrode is to be placed is rubbed with a little of the paste and the electrode applied to the head. This is held in place with a small patch of gauze soaked in paraffin of low melting point (Bioloid 47 to 49° C.). A low temperature hot plate (Sunbeam Model 14-B) keeps the paraffin at a constant temperature and ready for use. In the frontal and other regions devoid of hair, adhesive tape patches which have been warmed on the hot plate are used to hold the electrodes in place.

This method of electrode application is favored for infant sleep studies because:

1. The procedure is very fast (only a little slower than using bentonite "mud" alone), yet it gives a tight contact which will hold under very adverse conditions (seizures, movements of sleep, pillow rub, etc.).

2. The procedure causes very little disturbance or discomfort to the patient. (In many instances the electrodes were applied while the child slept.)

3. The electrodes may be applied satisfactorily in spite of considerable movement on the part of the patient.

4. Electrode artifact is a comparatively rare occurrence. Thus the necessity for changing "popping" or otherwise faulty electrodes, with the possibility of disturbing the child's sleep, is obviated.

Ten standard electrode placements are used routinely by us.[13] Further placements are made if the routine runs indicate the presence of focal activity in order to make a more circumscribed localization possible. Both scalp-to-scalp and ear-to-scalp recordings are employed.

The use of less than the eight bilateral lobar electrodes precludes the possibility of making an adequate coverage. However, the use of many more than the standard placements in children is unnecessary and decreases the likelihood of obtaining a satisfactory tracing because the prolonged procedure makes it all the more difficult for the child to endure.

The placement of a large number of electrodes such as is considered mandatory by certain authors not only tries the child beyond the limits of his endurance, thereby risking the possibility that no record whatsoever will be obtained, but is in all but an occasional case unnecessary because a focal discharging lesion in the characteristically labile brain of the child is generally reflected a considerable distance from its focus and can easily be recognized by a trained technician in the standard electrode proximal to it.[14] This especially applies to sleep.

*See Goldman[11] and Offner.[12]

In only one case* in the present series where there were definite signs of a focal nature in the neurological findings or character of the seizure or disclosed upon subsequent exploration or x-ray study was a discharging focus not detected and localized. This, of course, does not mean that some primary discharging foci were not missed in this series, but it does indicate a high percentage of detection at least equal to and possibly greater than the general results with the localization of focal lesions in adults as reported by the various laboratories in which large numbers of electrodes are employed routinely. It has been our experience that the placement of too closely spaced electrodes sometimes is a hindrance rather than a help in detecting certain types of lesions, especially large space-occupying neoplasms and hematomas, when the relative "silence" of the affected side in the region of the lesion and the relative activity, through reflection by way of the association fibers or through mechanical deformation of the opposite homologous region, can lead to a false lateralization.

It has been said that sleep makes the localization of focal lesions more difficult.[15] The opposite has been our experience. The sharp waves and the spiking activity produced by certain lesions (especially atrophic lesions in children) are usually increased in magnitude and extent during sleep, and tend to stand out more sharply against the slower background of the sleep pattern and are therefore more easily localized by phase-reversal techniques.[16]

In this series there were seventy-two strictly focal electrograms. In all patients explored surgically the localization was correct within the limits of surgical practicability.* Eleven subdural hematomas were detected and ten correctly localized; one bilateral hematoma was not recognized as existing on the less affected side. Two astrocytomas, one astroblastoma, three hemangiomas, and two brain abscesses were detected and correctly localized. One hemangioma was incorrectly lateralized to the opposite homologous region of its locus because of misinterpretation of a relatively silent area. In no instance in which the electrographic findings were negative for a lesion was one subsequently revealed by other means (x-ray, exploration, autopsy, etc.).†

More than one thousand subjects have been studied by this method during the past three years. This work is concerned with the establishment of the characteristics of the normal sleep patterns and their variations with age. The acceptability of a subject as "normal" is based on a negative personal and family history for neurological and mental disease, a physical and mental development consistent with chronological age, and a negative physical examination. As a further check it has been possible in a large percentage of cases to follow the subsequent development of the subjects for periods ranging from six months to three years.

THE PATTERN OF NORMAL SLEEP AND ITS VARIATION WITH AGE

Dissociation Between Hemispheres—Symmetry and Synchrony.—A charac-

*A 36-month-old boy with a capillary hemangioma and convulsogenic focus in the right motor strip and a similar lesion of the face on the same side.

*Within the field exposed by craniotomy.

†No children in this age group with suspected infratentorial or deep midline neoplasms have been referred to us for electroencephalography, and we have not therefore had the opportunity of studying sleep in such cases. In older children with space-occupying lesions of the posterior fossa, sleep has not proved of any assistance in detection or localization.

teristic of the normal adult electrogram, both in the waking and sleeping state, is the close symmetry between sides; that is, if the electrodes are carefully located so as to lie over homologous regions of the brain the activity of the two sides tends not only to be fairly symmetrical in terms of amplitude but also in terms of wave length and phase. In the newborn infant, however, this nice association between the two hemispheres is not so evident. Indeed, in a large proportion of newborn infants there appears to be a marked dissociation between sides. Greater correlation is evident within the first few weeks, but the progression toward the mature state is relatively slow and is by no means complete by the end of the thirty-sixth month.

As is the case with the ontogenetic development of activity in the various areas of the brain, the intimate association between hemispheres appears to progress more rapidly in some areas than in others. Thus, a fairly close correlation between sides first occurs in the central region, then in the frontal, then the occipital, and finally in the temporal regions. A fairly close symmetry and synchrony may be attained in the parietal regions before the end of the first month, although the 14 per second spindles may occur alternately, rather than synchronously, during the first four months. At the end of this time the parietal and frontal regions should show a reasonably close interhemispheric correlation. The occipital, and especially the temporal, traces may continue to show a definite dissociation up to the age of 35 to 40 months. Practically, the temporal leads present the greatest difficulty for interpretation because a fairly marked dyssymmetry may persist in this region in normal children during sleep until the age of 4 or 5 years. It is particularly important when reading infant sleep tracings to consider long stretches of the record at a time because short sections may give the impression of a very marked amplitude (abnormal) asymmetry in either the temporal or occipital leads which is in reality only an expression of the dissociation between sides. Thus in a short section of record one temporal lead may show an episode of fairly high voltage waves which may be coincidentally absent from the temporal trace of the opposite side. A study of the record as a whole, however, will show that the apparent amplitude asymmetry is in reality due to a lack of reciprocity of the activity of the two sides.

Spindles.—Ontogenetically, the first electrographic component of sleep to make its appearance is the so-called "sleep-spindle." Indeed, in the neonate the presence of spindles is sometimes the only characteristic by which the sleep and waking electrograms may be differentiated. Rhythmic sequences of 13 to 15 per second waves appear in light sleep as early as the first two or three days after birth (full-term infants). This activity has its origin in the region of the vertex bilaterally. Initially the spindles are poorly defined and of low amplitude, but with each succeeding week of life they become more clearly expressed and the characteristic spindle form becomes more evident. In most infants the spindles are quite strongly expressed by the third or fourth month (**Fig. 1**), but usually attain their ultimate form sometime between the twenty-fourth and thirtieth month (**Fig. 2**).

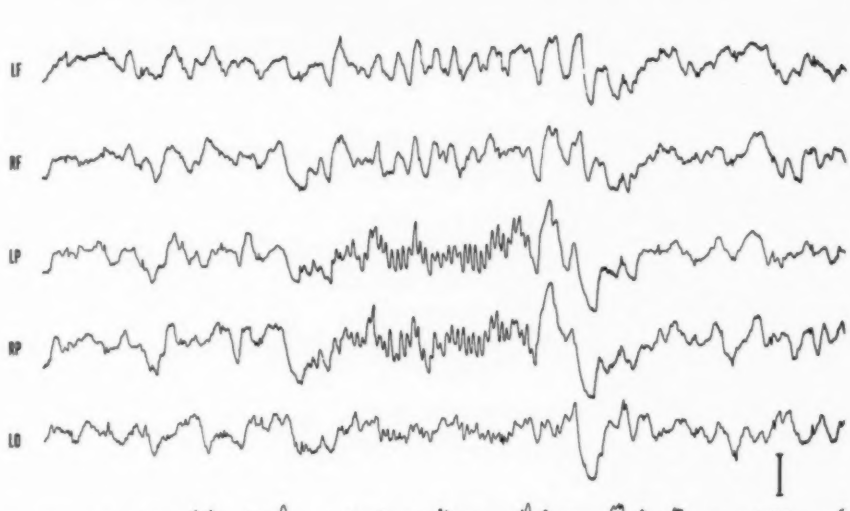

Fig. 1.—Aged 3 months. Clearly defined 13 to 14 per second vertex dominant spindles of moderately high amplitude.

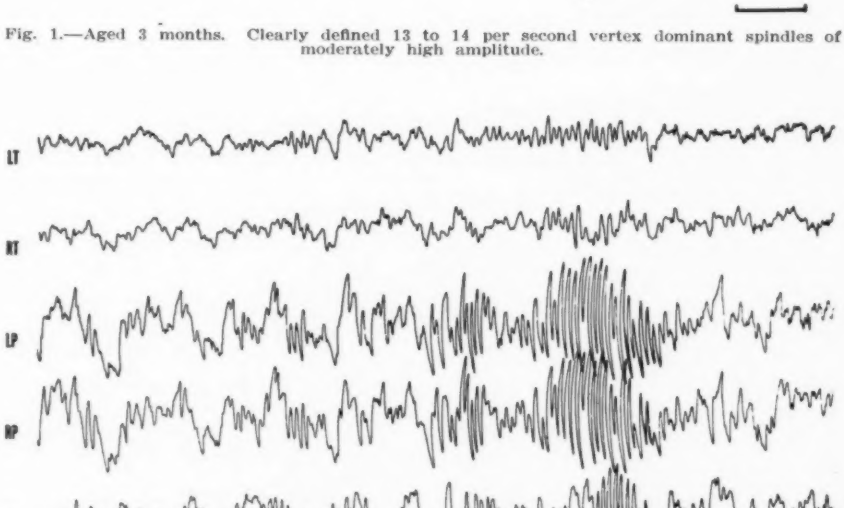

Fig. 2.—Aged 28 months. Very high voltage 13 per second vertex dominant spindles, a common finding at this general age level.

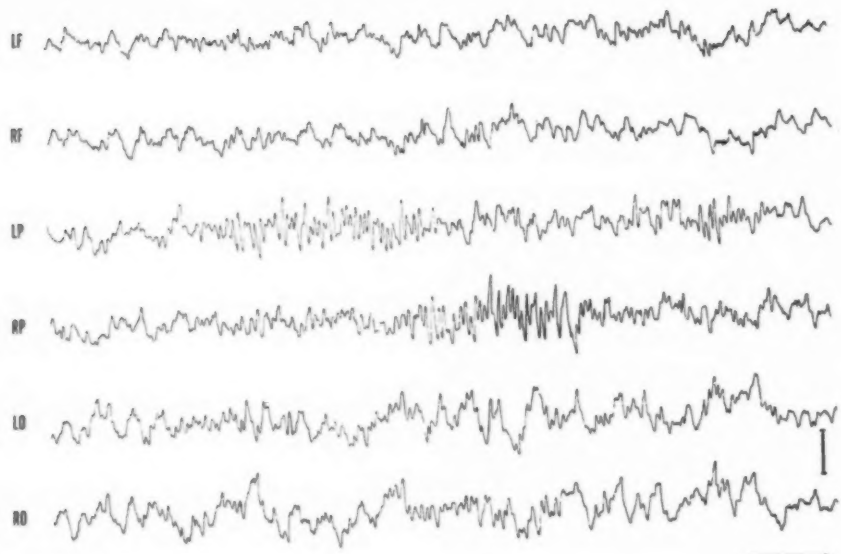

Fig. 3.—Aged 4½ months. Alternating spindle discharges in normal infant. Such dissociation is rare in children after the fifth or sixth month.

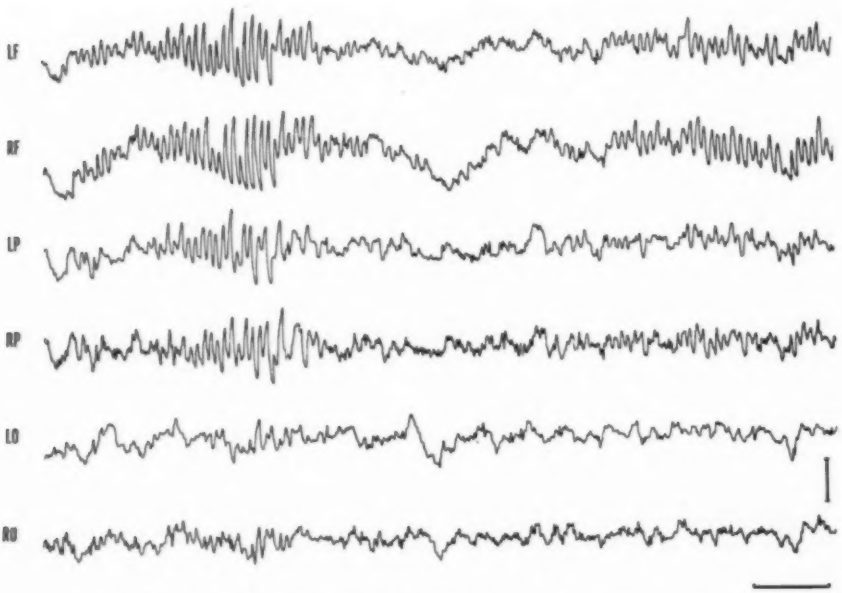

Fig. 4.—Aged 33 months. Frontal dominant 11-12 per second spindles.

As a rule the spindles appear in both hemispheres synchronously, but may occur alternately in homologous leads during the first two to four months (Fig. 3). The spindle frequency is remarkably constant from individual to individual, varying little from the mean of 14 cycles per second. The total range in the present series is not greater than plus or minus 1½ cycles per second, and in approximately 85 per cent of the cases the variation is not greater than plus or minus ½ cycle per second. This is true only if the frequency is measured in all cases in the same "light" stage of sleep, because in some infants the spindles slow in frequency progressively with deeper sleep. Characteristically, however, the spindles gradually disappear from the record without slowing appreciably. In the early, *spindle dominant*, phase the spindles are usually from 1 to 2 seconds in duration, but in very young infants durations of as long as 3 or 4 seconds are occasionally seen. The duration of the spindles usually decreases as sleep becomes deeper.

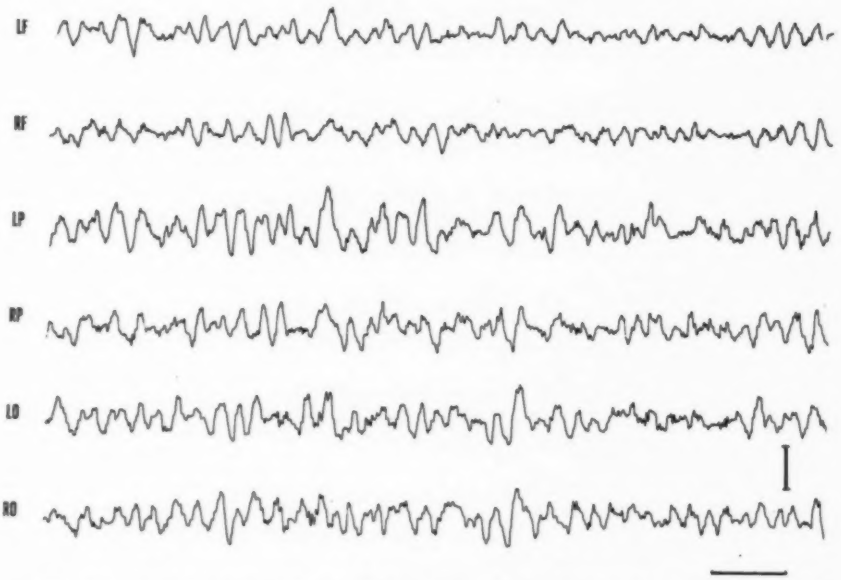

Fig. 5*A*.—Aged 9 months. Fast activity appears in the hypnagogic stage and gradually increases in amplitude in early sleep until it reaches a peak just prior to onset of the spindle stage (see *B* and *C*). The progression then reverses and the fast activity gradually diminishes in amplitude as still deeper levels of sleep are reached. Partial arousal results in reinforcement.

In the age group with which this paper is concerned, namely, birth to 36 months, *the 14 per second vertex dominant spindle* is the only type of spindle which is commonly observed. In older children (after the age of 4 or 5 years) a slower, approximately *12 per second frontal dominant spindle* is sometimes seen. There were only three cases in our birth to 36 months age group which showed definite examples of spindles of the latter type (Fig. 4).

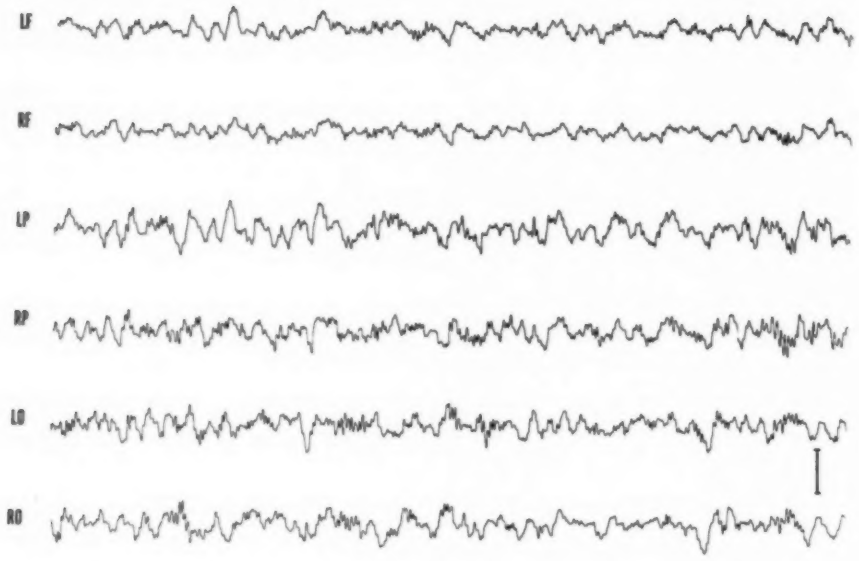

Fig. 5*B*.—Increase in amplitude of fast activity in the same infant with onset of light sleep. Note disappearance of rhythmic hypnagogic activity.

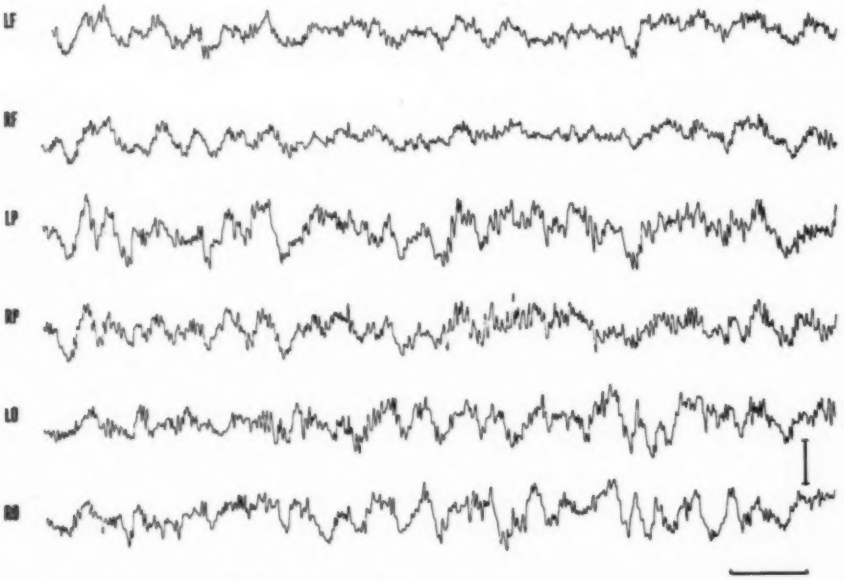

Fig. 5*C*.—Maximum amplitude of fast activity in the same patient just prior to appearance of spindles.

Fast Activity.—Sometime between the fifth and sixth month many infants begin to show a low voltage fast activity in the early stages of sleep. This activity occurs in all leads but is most pronounced in the central or post-central regions (Figs. 5*A*, *B*, *C*). The frequency averages approximately 25 cycles per second, but varies as much as plus or minus 6 cycles per second in different subjects. When it first occurs the amplitude of the fast activity is very low, 5 microvolts or less, but relatively high amplitudes (30 microvolts maximum) may be seen by the twelfth to the eighteenth month when it seems to reach its maximum expression. After the age of 30 to 36 months much fast activity in early sleep is less common and generally the amplitudes seen are not as great as in the 12- to 18-month age group. Older children are much less likely to show fast activity in early sleep, and after the age of 7 years it is relatively uncommon.

Hypnagogic Hypersynchronous Phase.—It is we'l known that the waking electrogram of the newborn infant has an essentially base line character.[16-23] The first rudimentary signs of the ultimate rhythmic nature of the electrical activity of the brain are manifested only during a variable so-called "drowsy" period just prior to the onset of true sleep. At this time, poorly defined, low amplitude oscillations of inconstant period occur in the vertex region bilaterally.*

With each succeeding month of life these oscillations assume a more constant period, become greater in amplitude, and longer in sequence. When they first appear they may show a wide and irregular frequency modulation between 2 and 5 cycles per second, but with increasing age they become faster and show greater regulation of both frequency and amplitude. Their areal distribution also tends to become more generalized.

For the first three months the hypnagogic, or "drowsy," waves occur predominantly in the central region and are reflected at a much lower amplitude in other regions. An extension of the distribution appears to occur in an anterior direction during the next few months so that the frontal leads tend to show them in long serials and at high amplitude while the occipital leads may show less organized activity (Figs. 6*A* and *B*). However, it is important to realize that this basic schema shows considerable variation both from patient to patient and at different times in the same patient. The pattern is determined somewhat by each of the following factors: (1) whether or not the child becomes deeply asleep gradually or precipitously; (2) how much of a dominant occipital rhythm the child has developed—a very variable factor. Thus once the occipital alpha rhythm becomes definitely established (as early as 4 months in some children but invariably by 9 months in all normal children) three basic variations of the development of the hypnagogic hypersynchronous phase are observed:

In the simplest of these, as the child progresses toward sleep, the occipital alpha rhythm gradually slows and increases in amplitude. The occipital region appears to maintain its position

*These waves were originally described by Smith[20-22] who designated them "drowsy" waves because of their occurrence just prior to the onset of sleep. We prefer to use the term "hypnagogic activity" in order to avoid the confusion which may arise from the fact that young children may be in this phase electrographically without showing objective evidence of *drowsiness* as this state is generally defined. It is recognized that the two terms mean essentially the same thing but the more common word "drowsy" conjures up a mental picture that the less used "hypnagogic is less likely to produce. (See also a more recent note by Dole and Busse.[24])

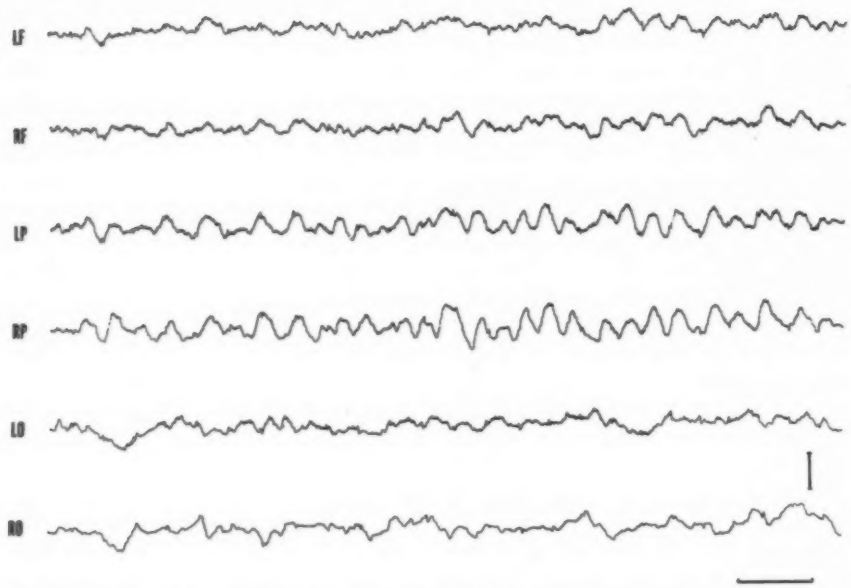

Fig. 6*A*.—Relatively low amplitude hypnagogic activity predominantly in the vertex region in child 8 weeks of age. Compare Fig. 6*B*.

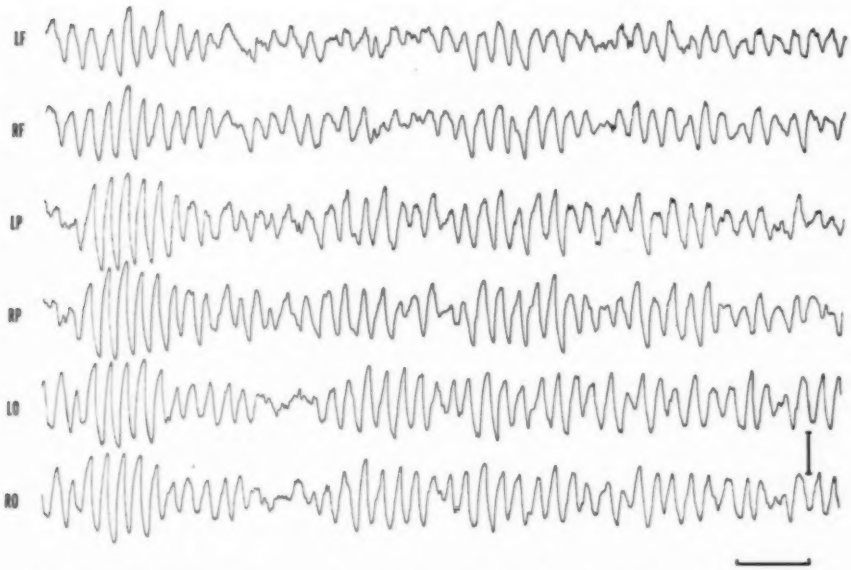

Fig. 6*B*.—Continuous hypnagogic hypersynchrony in the same child, aged 35 months.

of "pacemaker" and the record reveals a rhythmic sinusoidal activity involving all leads, greatest in amplitude in the occipital region, next in the central, and lowest in the frontal and temporal regions (Figs. 7*A, B, C*).

This slowing of the basic rhythm can occur over a relatively long period and it is clear that it constitutes a liable criteria, for indeed they may be a side feature in this period. As will be shown later, a normal child, after arousal from sleep, may lie on the bed, eyes open and smiling, and with every appearance of full wakefulness at a time when the electrogram is showing continuous high voltage 4 to 5 per second serials in all leads.

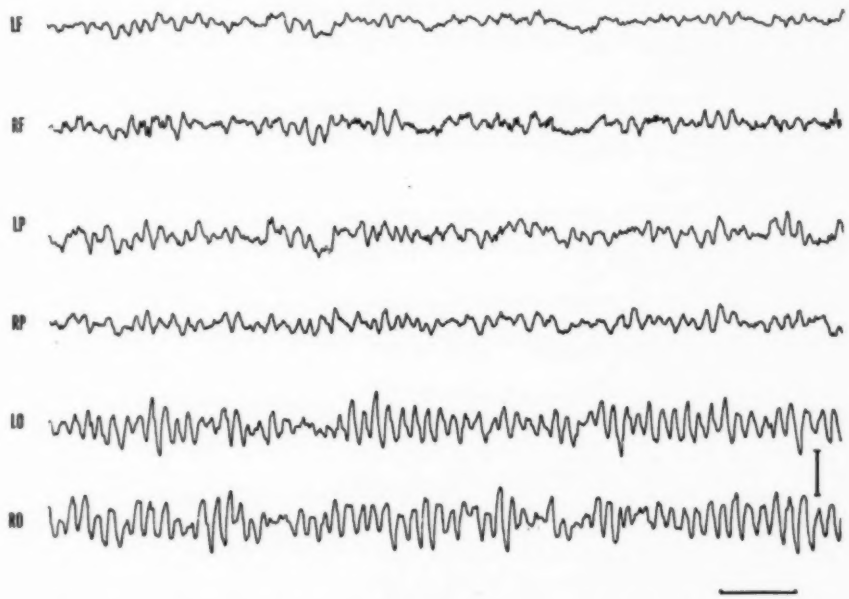

Fig. 7*A*.—Aged 10 months. Gradual slowing of the occipital alpha during hypnagogic stage with gradual development of hypersynchrony and some shift of dominance anteriorly. Patient fully awake. Note well-regulated occipital alpha of 6 to 7 per second.

serious hazard in the interpretation of waking records in very young patients, for it has been definitely established that infants and young children may go in and out of the hypnagogic state without actual sleep ever eventuating. The problem is further complicated by the fact, stressed earlier, that it is often not possible to determine clinically with any certainty whether or not a child is in the predormant state: restlessness and irritability are not reliable criteria, for indeed they may be a side feature in this period. As will be shown later, a normal child, after arousal from sleep, may lie on the bed, eyes open and smiling, and with every appearance of full wakefulness at a time when the electrogram is showing continuous high voltage 4 to 5 per second serials in all leads.

Another course which the electrical pattern may take in the hypnagogic phase is very similar, qualitatively at least, to that which occurs in the adult during the same period. This variation is characterized by the fact that the continuity of the occipital rhythm begins to break up without marked slowing. The occipital traces begin to assume a more base line character. As the same time, and even in some instances before a noticeable disruption

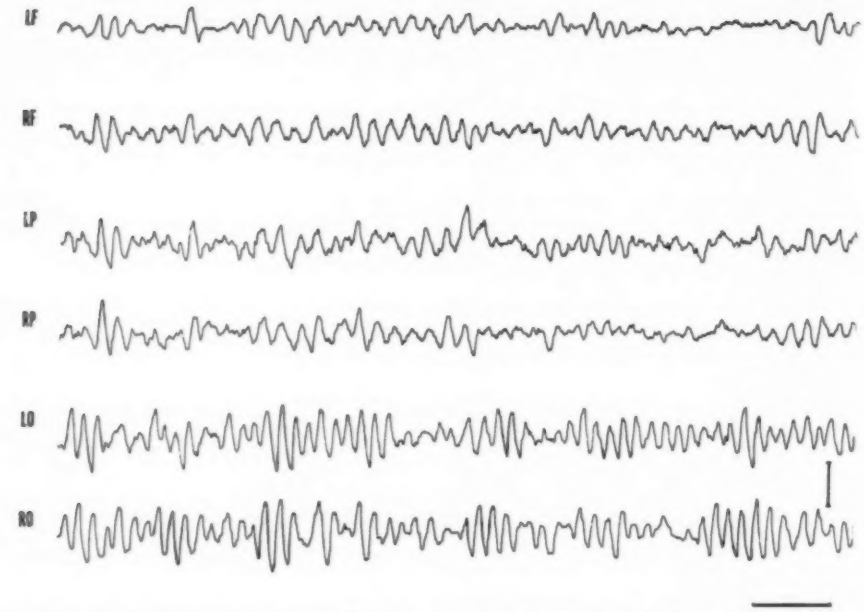

Fig. 7*B*.—Same patient more "drowsy." Alpha has slowed approximately ½ cycle per second. Note increased slowing anteriorly.

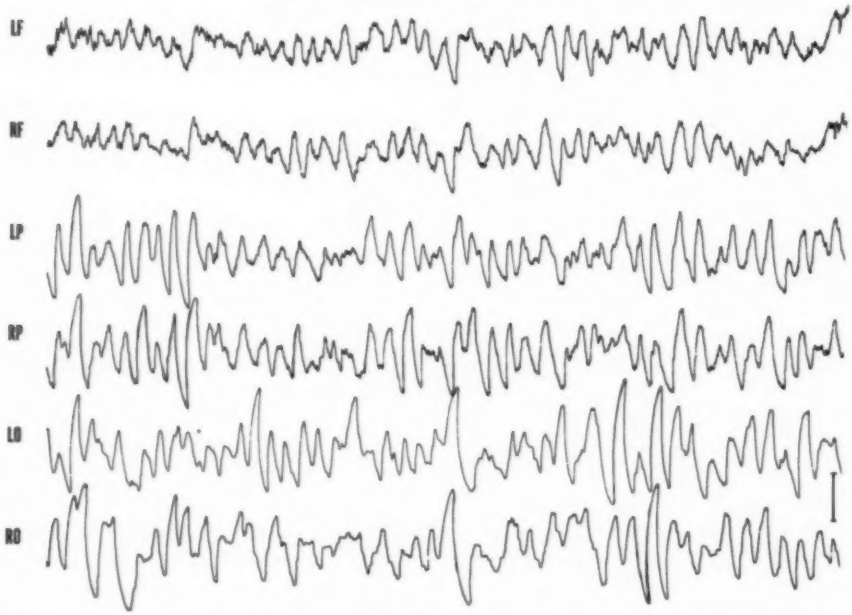

Fig. 7*C*.—Same patient just prior to onset of true sleep. Note that the amplitude is still maximum in the occipital region, but that rhythm is more constant in central and frontal leads.

of the alpha continuity occurs, the central and, to a lesser degree, the frontal regions begin to show the bicentral hypersynchronous rhythm of the oscitant phase, which becomes more and more strongly expressed as the alpha rhythm becomes progressively less evident (Figs. 8 *A* and *B*).

These two variations of the predormant electrical pattern may be seen at any time between the ages of 4 months and 4 years. Another variation also is seen but only in the older infants. It makes its first appearance at approximately fourteen months, but is more common and tends to be more pronounced between the ages of 3 and 5 years. The onset of the hypnagogic phase is signaled by a general reduction in the amplitude and rhythmicity of the activity of all areas. This relative "quiet" may then be broken by paroxysmal bursts of high voltage sinusoidal waves which involve all leads but which are greater in amplitude in the precentral or central regions and generally more strongly expressed in the frontal than in the occipital regions (Fig. 9).

These paroxysmal bursts may reach extremely high voltages when maximally expressed (in excess of 350 microvolts) and therefore constitute a possible source of error both for the interpretation of sleep where this is sought and for the interpretation of waking records where the oscitant state may intervene without true sleep ensuing.

Because of this, we have found it necessary to adopt a rather rigid policy regarding the evaluation of such activity in children of 30 months to 10 or 11 years, the age group in which the phenomenon is most likely to occur. The appearance of such bursts in the period just preceding true sleep, or at its onset, or at a time when the electrogram shows other evidence of the hypnagogic state, is never considered an epileptiform manifestation unless accompanied by spike discharges in some form. Long experience has shown that if a patient with established petit mal epilepsy shows abnormal paroxysmal activity during sleep the spike component is always strongly in evidence and the epileptiform serials persist into fairly deep levels of sleep. A distinguishing characteristic then of the pre-oscitant paroxysmal episodes is that they make a brief appearance at the onset of sleep and do not persist into the deeper stages.

The fact that young children may slip into nonrecognized hypnagogic states has been noted by other electroencephalographic laboratories when large numbers of children are seen. The Brandts,[25] particularly, have drawn attention to the fact and pointed out that it is a much more reliable procedure purposely to seek sleep by providing conducive conditions and perhaps by the use of sedation, so as to reduce the likelihood of misinterpretation by preparing the technician and electroencephalographer for the advent of such changes.

It should be pointed out that it is not uncommon to see cases in which a combination of these classic variations of the hypnagogic activity occurs. Thus it may be that the child may show initially a general slowing and continuous hypersynchrony (first variation) which may then give way, as true sleep is approached, to relatively low voltage, aperiodic episodes which in turn may be interrupted by short paroxysmal high voltage serials (third variation). As will be seen when we discuss

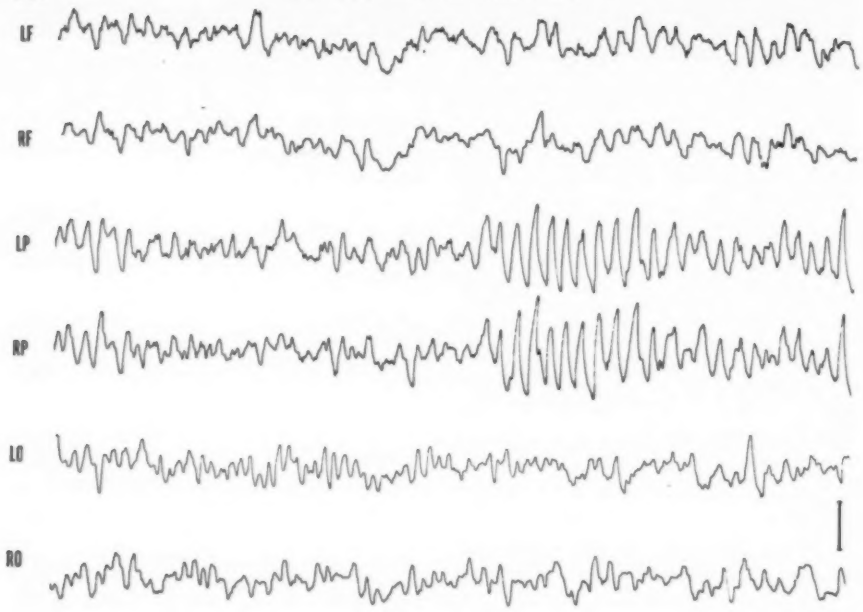

Fig. 8A.—Aged 34 months. Occipital alpha beginning to thin out with appearance of high voltage 4 to 5 per second serials in the central region.

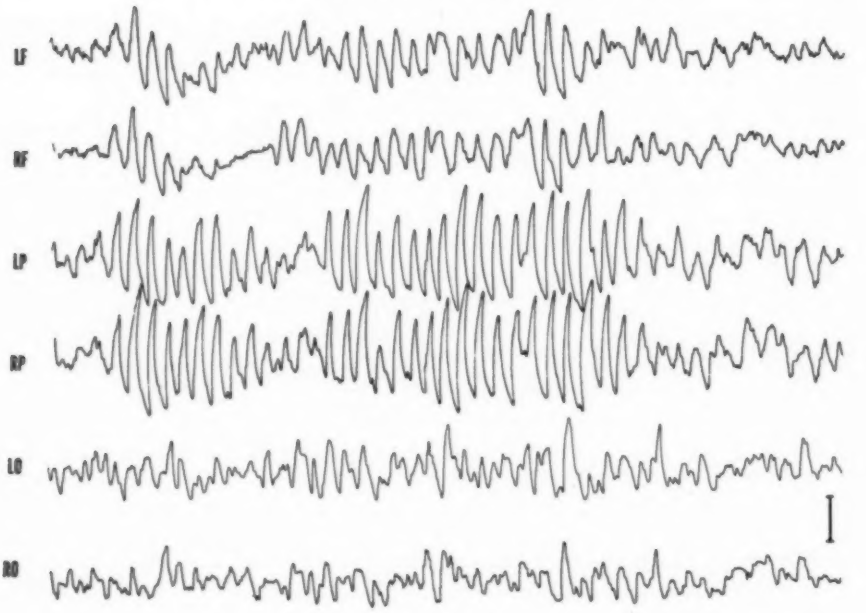

Fig. 8B.—Same child just prior to onset of true sleep. Note the high voltage hypersynchronous activity in the central leads and the polyrhythmic much lower activity in the occipital leads. The alpha rhythm is difficult to identify.

arousal, such patterns probably represent transitory reversions or waxing and waning of the sleep process.

Another variable which appears to be more closely related to age than the variations in pattern is the factor of frequency. Generally speaking, it can be said, like the alpha rhythm, the hypersynchronous waves of the hypnagogic state increase in frequency with increasing age. In the adult the waves have a frequency of about 4½ to 5½ per second and the voltages rarely exceed 150 to 160 microvolts (more generally 80 to 110 microvolts). In the newborn infant, it will be recalled, the rudimentary drowsy waves are irregular in period and amplitude and the frequency variation is fairly wide, between 2 and 5 per second. The waves increase in frequency and amplitude and assume a more stable frequency characteristic with increasing age, reaching a peak expression sometime between the tenth and fourteenth month. In some normal children the maximal expression of the phenomenon is delayed until as late as 32 months. During the next few years the amplitude of the activity tends to decrease, but very little increase in frequency seems to occur, so that one expects to see the adult form by the tenth to twelfth year.

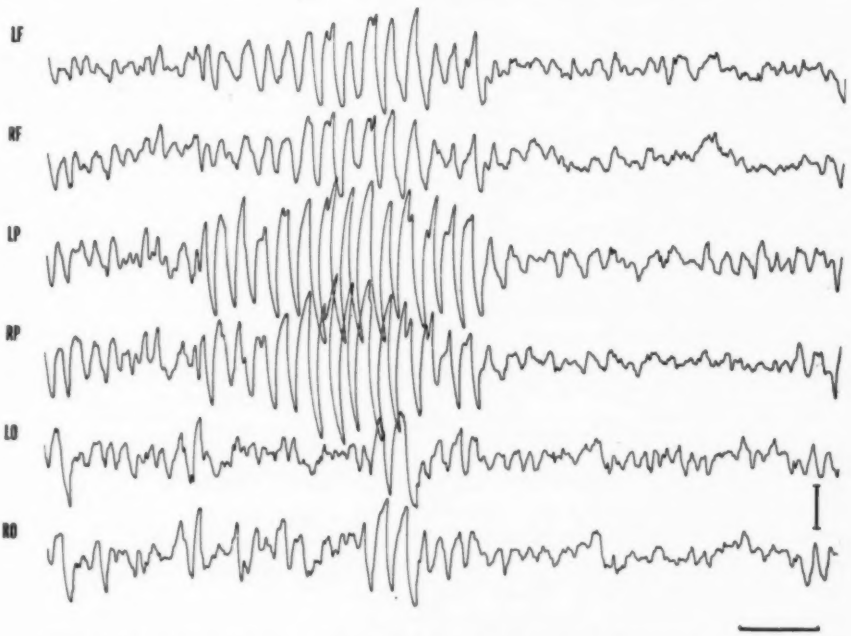

Fig. 9.—Aged 35 months. Paroxysmal high voltage slow serials occurring just prior to onset of true sleep. This particular sample was chosen to illustrate the fact that these paroxysmal bursts are not always sinusoidal, something having notched tops suggestive of epileptiform discharges.

Central Sharp Wave Transients.—In many subjects after the age of five or six months, the onset of true sleep is marked by the appearance of bilaterally synchronous sharp wave transients in the region of the vertex.

These waves may occur singly or in short aperiodic series (Figs. 10*A*, and *B*). At about the age of 36 months, when they are the most pronounced, the waves are usually diphasic in form, very high in amplitude, and often quite sharply peaked. The initial, negative, phase has a duration of about ⅛ second; the successive, positive, phase is usually a little more prolonged, averaging approximately ⅙ to ⅐ second, but this is subject to considerable variation. As with most high voltage rapid transients in the electroencephalogram, the sharp diphasic wave is often followed by a slow (negative) afterswing of lesser amplitude.

Although there is some variability, these sharp wave transients are generally the first sign of the onset of true sleep. The next stage is marked by the appearance of spindles and it is interesting to note the apparent relationship between these and the sharp waves. Initially there is usually a phase during which the spindles and the sharp waves occur in close association, the sharp waves always preceding the spindles so as to give the appearance of a sharp transient followed by a series of decrementing oscillations as in a highly tuned system with a low-damping factor. This is followed by a period in which the spindles appear without the preceding sharp wave, but unless partial arousal occurs the sharp waves usually do not occur again without an associated spindle discharge.

It was mentioned above that the central sharp waves are very clearly delineated at the age of 36 months. There is a progressive development of the pattern up to that time. After the age of 3 to 4 years the pattern again becomes gradually less pronounced. Rudimentary bicentral sharp waves are seen in light sleep as early as the third or fourth month; there is a progressive increase in definition and amplitude thenceforward until the maximum expression of the phenomena is reached sometime between the third and fourth years. From this time onward there is a gradual attenuation of amplitude and form, such that the initial negative phase often becomes a little shorter in wave length but less sharply peaked, and the succeeding positive phase much less pronounced. This transformation progresses quite rapidly during the period from 3 to 13 years, at which age the adult form is reached, and then levels out during the next thirty to forty years. After fifty the sharp wave transients, and to a lesser degree the spindles, may be very rudimentary or entirely absent.

The point should be stressed that the bicentral sharp waves of light sleep are spontaneous and therefore are to be distinguished from the K complexes originally described by Davis and associates[26] which by definition are transient electrographic responses to applied sensory stimuli.[27] Whether there is any real physiologic distinction to be made has not been definitely established. The original authors reported that K complexes often appeared apparently spontaneously in the lighter stages of sleep and several other investigators have referred to the spontaneous sharp waves as K complexes.[28, 29] Certainly the evoked and the spontaneous waves have some characteristics in common. They both occur at a maximum in the region of the vertex bilaterally; their wave configuration is similar, and they both are maximally expressed in the early stages of light sleep. The evoked response, or K complex, however, generally tends

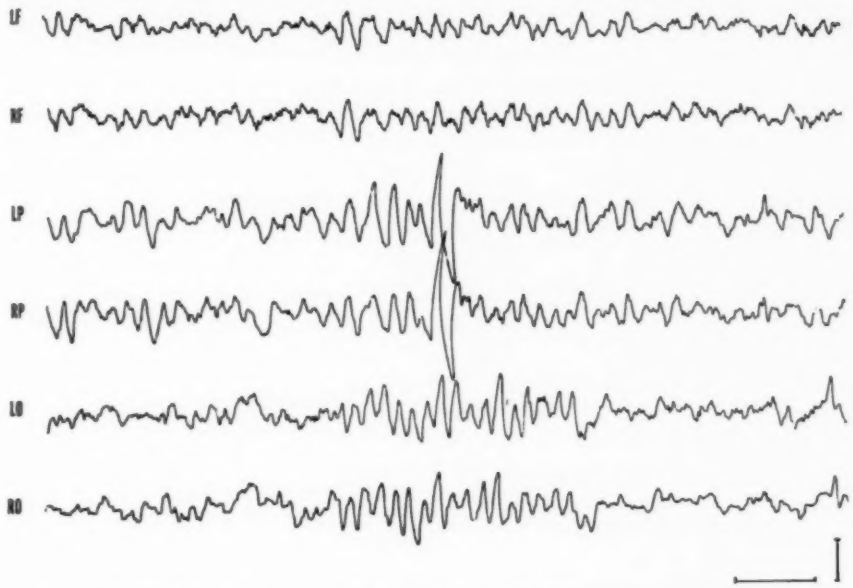

Fig. 10*A*.—Aged 35 months. Single diphasic sharp wave transient occurring at time when drowsy waves are still present. This was the initial wave of this type to appear in this record.

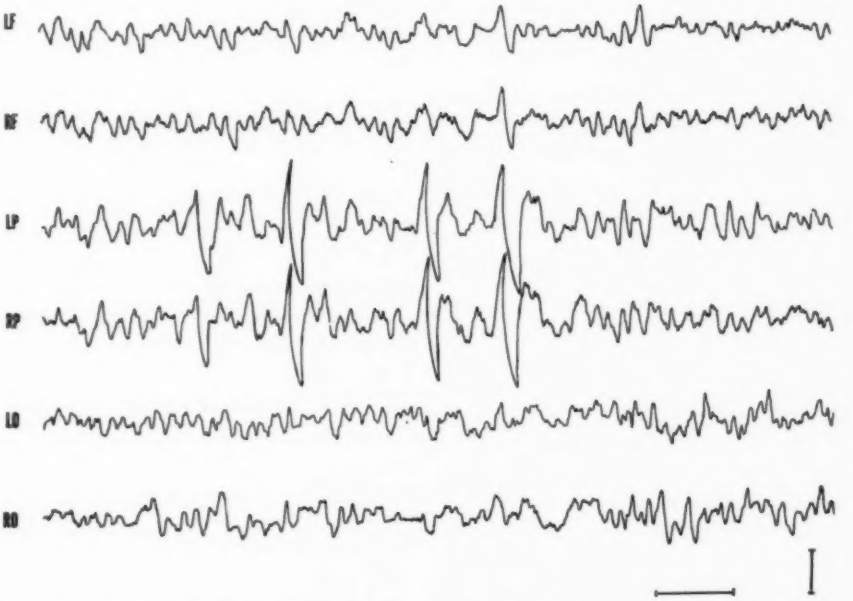

Fig. 10*B*.—Same patient 30 seconds later. Note series of recurrent bicentral sharp wave discharges. In the next stage of sleep the 4 to 5 per second activity present in this sample disappeared, and the sharp waves occurred in association with sleep spindles.

to have a longer wave length and be less sharply peaked than the spontaneous transients (Fig. 11). Also, like the "secondary discharge" of Forbes and Morison,[30] the K complexes can only be elicited within a certain time sequence as each response is followed by a relatively long refractory period.

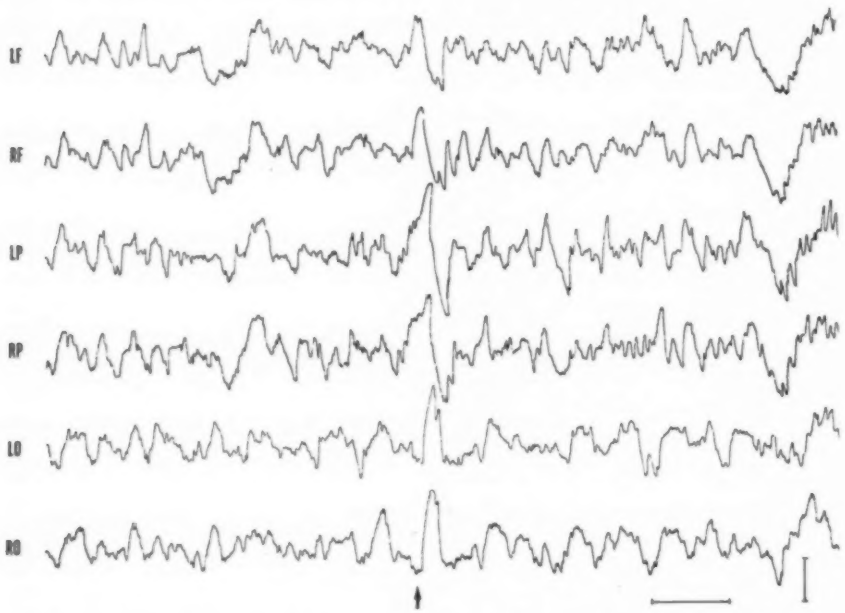

Fig. 11.—Aged 14 months. Sharp wave response to loud sound stimulus (handclap).

On the other hand, the spontaneous bicentral sharp waves often occur serially, spaced at quite brief intervals (Fig. 10*B*). Furthermore, while the spontaneous wave transients tend to be rather sharply localized to the central region, the evoked transients appear to involve a much wider areal response (Fig. 11).

Davis and co-workers have suggested that the spontaneous waves are merely self-evoked K waves arising as a result of stimulation by the sleeper's own breath sounds, etc., at a level of unconsciousness at which the action of the afferent system upon the brain is still highly effective but not effective enough to cause complete arousal. Regardless of whether or not this is true, it is clear that the appearance of the spontaneous sharp waves marks a definite change in the physiologic status of the individual, because stimuli, either intrinsic or extrinsic, fail to elicit such responses in the earlier drowsy or presomnolent stages of the sleep process.

Practically speaking, the central sharp wave transients are a possible source of misinterpretation.[31] Indeed, some authors[32] have been led to discourage the use of sleep for diagnostic purposes on this basis. But while the admixture of spindle activity and sharp wave forms in the central region can give rise to many bizarre and epi-

leptoid-appearing wave configurations* it is not difficult with experience to distinguish these from true convulsive activity. Nevertheless, it cannot be overstressed that the electroencephalographer should have a wide experience of normal sleep records, especially those of infants and young children before attempting to use sleep in routine clinical practice.†

Activity of Arousal.—Loomis and co-workers[27, 33] were the first to show that reactive arousal involved a more or less complex electrographic pattern rather than a simple immediate transition from "sleep" to "waking" activity. They reported that this consisted of an initial diphasic slow wave followed by a series of rapid oscillations of "about 8 to 14 per second," the total pattern occurring maximally in the central region but appearing at lower amplitude in the frontal, occipital, and temporal areas also.

This phenomenon tends to be very strongly expressed in children but varies somewhat in character and in degree with age. The initial slow component, sometimes erroneously referred to as the K complex,‡ has been discussed elsewhere in relation to the spontaneous bicentral sharp wave transients of early sleep. The "fast" component represents, as was hinted by the original workers, a process associated with a greater degree of arousal. Thus, the slow component may appear alone, in response to an applied stimulus such as a loud sound, without clinical signs of arousal and indeed without transition to a lighter stage of electrographic sleep (Fig. 11). The fast component, on the other hand, is always associated with clinical or electrographic evidence of partial or full arousal.

Neither component of the electrographic arousal reaction is clearly defined before the age of 2 months. During the first eight weeks of life little or no electrographic response can be evoked by intense stimuli even though clinical arousal results. At this time, and especially during the first six weeks, the transition from sleep to waking is characterized by only a flattening of the electrographic traces. Sometime between the eighth and twelfth week rudimentary diphasic slow wave responses to applied stimuli may occur, and it is about this time also that the first signs of a definite rhythmic hypersynchrony similar to that of presleep make their appearance in the post-arousal stage. However, the slow component of the arousal reaction is rarely well defined before the twenty-second week.

The faster component of the arousal reaction is usually not seen before the age of 7 months. Initially it is quite rudimentary and consists of few moderately high voltage sinusoidal waves of about 4 to 4½ per second superimposed on a slower irregular background.

From the age of 7 to 8 months there is a gradual but consistent increase in the amplitude and extent of the arousal pattern so that by the thirteenth month the reaction is quite marked. Very high voltage prolonged arousal reac-

*Especially with interscalp electrode recording.

†The variations of the patterns of sleep in adults are comparatively simple and may be easily recognized with very little experience. The variations in children, however, are much more complex and it is much easier to be misled. This problem will be discussed at greater length in Part II of this paper under the heading "Criteria for Minimum Acceptable Abnormalities in Sleep."

‡According to the original workers' definition the term "K complex" was used for both the slow and the "fast" components of the arousal reaction.[33]

tions occur during the next two to three years and then gradually the phenomenon seems to decline until the adult form is reached (sometime between the twelfth and fourteenth year).

The configuration of the arousal reaction is subject to some variation even in children of the same age and

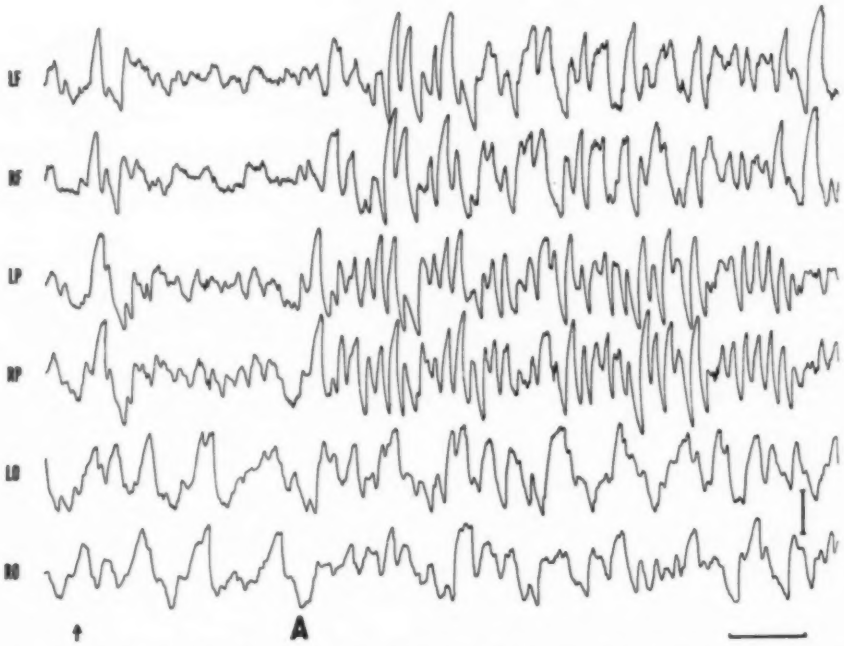

Fig. 12*A*.—Aged 17 months. All components of the arousal reaction present. Response at arrow elicited by loud handclap. This represents the sharp transient wave response to stimulus. At *A* another handclap elicits a similar response, but arousal ensues. Note appearance of burst of high voltage 5 to 7 per second activity chiefly in the vertex leads.

in the same child with varying depths of sleep. Essentially the fully developed pattern is similar to that shown in Fig. 12*A*. Note the initial slow component present in all leads followed by a higher frequency rhythm superimposed on a shifting base line and a slower less constant rhythm. The slow wave component is often obscured by the onset of the faster pattern and may not be easily seen unless it precedes the second component by a reasonable period. The faster rhythm varies in frequency from about 4½ to 7½ cycles per second depending upon age. In the age group with which we are concerned here it rarely exceeds 6 cycles per second. The duration of this component is also quite variable; usually it lasts from about one-half to four or five seconds, but sometimes it may be a dominant feature of the record for as many as thirty or more seconds.

The characteristics of the arousal response suggest that its two components are independent entities, the second of which is causally related to the first. The slow transient appears to be a sign

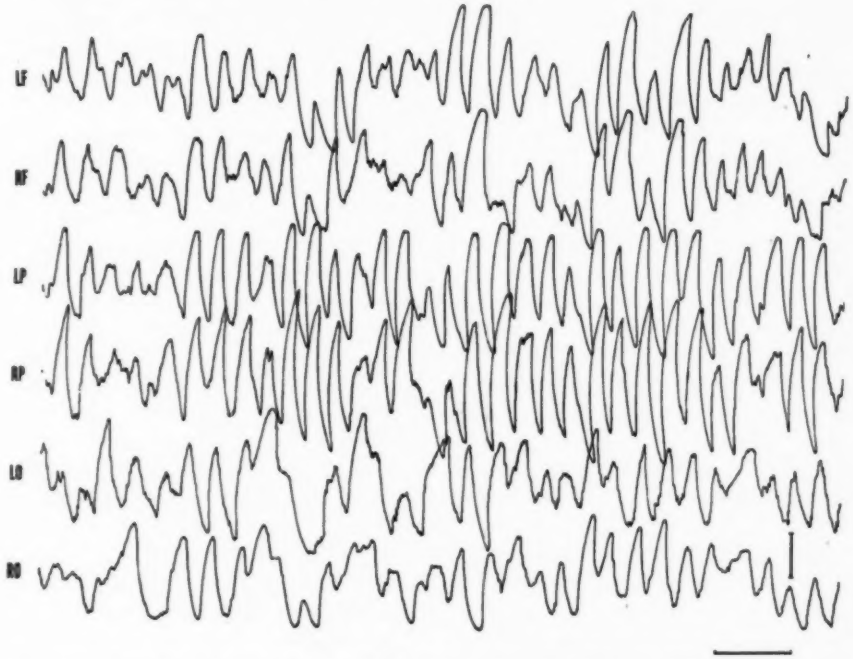

Fig. 12*B*.—Immediately following Fig. 12*A*. Note continuous extremely high voltage slow 3 to 3½ per second activity chiefly in the vertex and frontal leads.

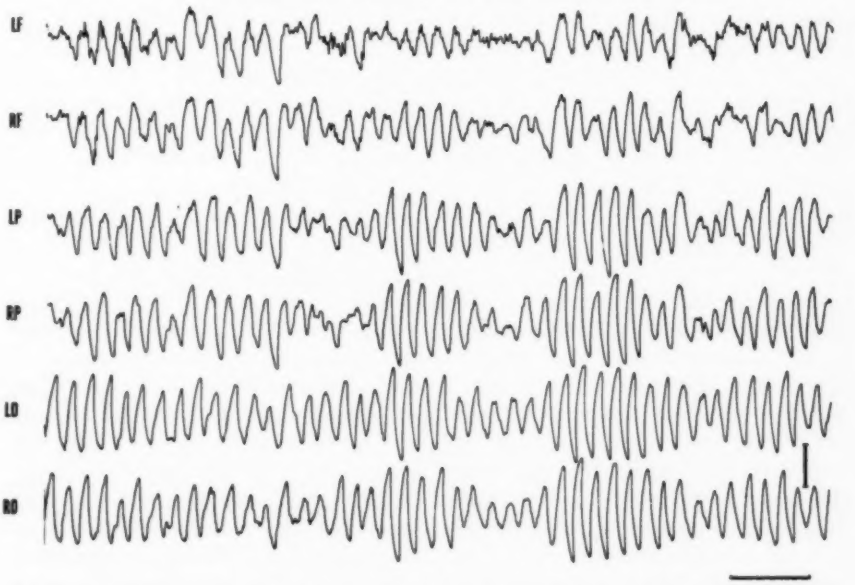

Fig. 12*C*.—Thirty seconds after Fig. 12*B*. Record now dominated by a 4 to 5 per second hypersynchronous rhythm involving all regions, but greatest in amplitude in the occipital leads.

of the primary afferent process activated by the stimulus—similar to the effect described by Forbes and co-workers in the anesthetized cat. The fast component possibly represents a reaction to the first and is a manifestation of the actual arousing (reticular?) process. Interestingly, the postarousal, or awakened, pattern in the young child is much slower than this component of the arousal response, and, as was pointed out before, is similar in character to the rhythmic hypersynchrony of presleep and is probably representative of a similar cerebral state. These apparently independent processes of arousal suggest some interesting relationships to the recent work of Lindsley, Magoun, and associates[36, 37] with reference particularly to the separation of the sensory and intrinsic (reticular) components of the arousal mechanism in experimental animals.

Postarousal Hypersynchrony.—Following the arousal reaction, if awakening ensues, a high voltage sinusoidal rhythm similar to that of the presleep period makes its appearance. At first this activity is predominantly frontal and is reflected to a progressively lesser extent posteriorly (Fig. 12*B*). As the child becomes more widely awake the dominance shifts gradually toward the back of the head and the frequency of the activity increases, thus constituting a simple reversal of the process seen in the presleep stage when the dominance shifts anteriorly and the waves decrease in frequency. (Compare Figs. 12*B* and *C*. The transition is often much more pronounced than this.)

It will be recalled that during the first six to eight weeks of life the transition from sleep to wakefulness is marked electrographically by a flattening out of activity rather than a hypersynchrony. Sometime between the eighth and the twelfth week some fairly rhythmic postarousal activity occurs but, oddly enough, it is usually most marked in the parieto-occipital region. It is not until the fourth or fifth month that a sustained postarousal sinusoidal rhythm is seen. Thenceforward it becomes gradually more pronounced; the rhythm becomes greater in amplitude, more stable in frequency, and more sustained (Fig. 12*C*). The phenomenon appears to reach a peak expression in most children some time between the twelfth and eighteenth month, but a very pronounced postarousal hypersynchrony is encountered in normal children as late as the fourth and fifth years. Generally speaking, the trend is toward a decline in the degree of expression of the phenomenon after the age of 24 months. Coincidentally there is a gradual increase in the frequency of the rhythm from an initial 3 to 4 per second when it first appears to about 5 to 5½ per second in the older children (Fig. 13).

Influence of Sedation.—The question has been raised, particularly by Liberson,[34] whether or not some of the phenomena herein described are the result of the action of the barbiturate employed to produce sleep. Liberson[34] indeed has suggested that the hypersynchronous activity of the pre- and postsleep stages is a direct effect of the action of the drug. We have investigated this problem by comparing in a large number of infants sleep produced with the assistance of small doses of Nembutal with that occurring naturally.

These studies have shown that sleep produced with the aid of mild sedation, such as has been used in the work reported here, does not differ essen-

tially from "natural" sleep. Indeed, the only effects which even relatively large doses of Nembutal seem to produce are an increase in fast activity and a decrease in the tendency for epileptiform activity to make its appearance. There is no doubt, however, that even small doses of Nembutal tend to enhance the fast activity already present, and as we shall see in Part II of this work children with certain types of diffuse cerebral pathology tend to show a much more marked response to Nembutal, in that it produces much more fast activity than it does in normal children.

However, it seems probable that children who have been sedated are much more likely to remain for long periods in the postsleep hypnagogic state than children aroused from natural sleep. Hence sedation may tend to increase the duration of the postsleep phase of hypersynchrony, but it does not enhance the expression of the phenomena. In the age group where postarousal hypersynchrony is strongly expressed, a child who has not been sedated may show as much or more than another child of the same age who goes to sleep without the aid of drugs. Similarly, the same child may show essentially the same degree of postarousal hypersynchrony whether or not sedation has been given.

The use of barbiturates or other drugs to produce deep hypnosis or light anesthesia, as, for example, by the use of intravenous Pentothal, is of very limited usefulness. When this

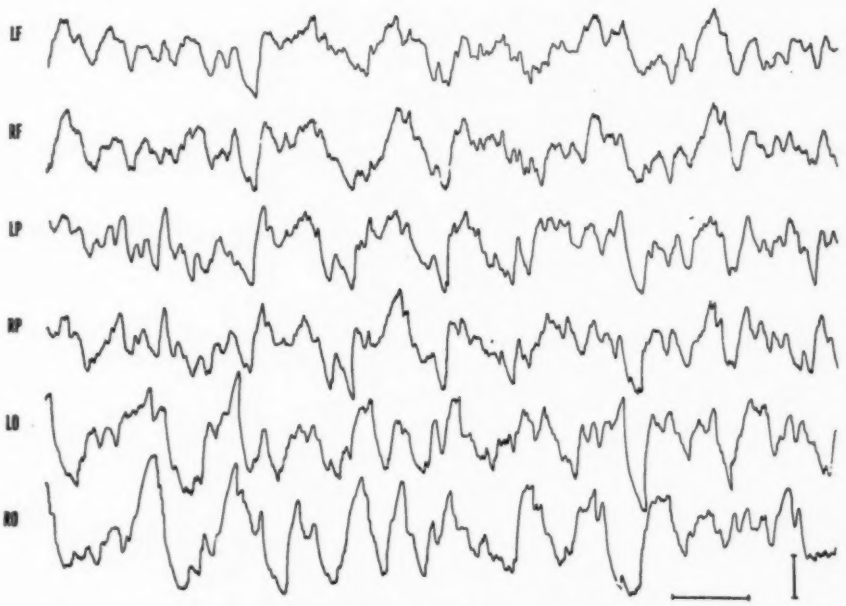

Fig. 13.—Aged 16 months. Deep sleep. This stage is always characterized by high voltage aperiodic slow activity, but nearly all frequency elements of the sleep process may be present. The pattern varies very little with age except that in young children it is much higher in amplitude and more polyrhythmic than in adults.

study was begun over three years ago, various drugs were tried, including Amytal and Pentothal in this fashion and the method eventually discarded because it proved to be quite unsatisfactory. Intravenous administration of narcotic agents requires, in addition to the regular technician, the presence of a specially trained and experienced person with the authority to carry out such procedures. The method itself also has several inherent faults, the most obvious of which is the fact that older infants often will struggle to avoid taking the needle, and may dislodge or loosen electrodes which have taken considerable time and patience to apply. Especially important is the fact that the initial stage of true sleep, which is the most productive phase, is not identical with the inductive period of drug narcosis, which is largely dominated by high voltage fast rhythms in all head leads and is relatively unproductive. Experience in a large number of patients has shown that epileptiform activity other than certain spike foci* tends to be depressed rather than enhanced by the use of drugs in doses sufficient to produce narcosis or light anesthesia.

SPECIAL NOTE

This is to acknowledge the fact that much of the material reported in this paper has been previously presented in tabular form by Dr. and Mrs. F. A. Gibbs in the recent edition of their *Atlas*.

No comment or comparison with their data has been made in order to emphasize the independent approach and to avoid extended discussion of minor inconsistencies and differences of terminology. The present report represents the first part of a serial and longitudinal study of normal and abnormal infants which has required several years to complete. It is concerned with a much greater number of cases within a much narrower age span than presented by the Gibbses and is considered to constitute a complementary addition to their more panoramic all-inclusive view.

*See also Fuster, Gibbs, and Gibbs.[25]

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INTRASPINAL TUMORS IN CHILDREN RESEMBLING ANTERIOR POLIOMYELITIS

Report of Three Cases

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IT SHOULD be re-emphasized, from time to time, that other conditions than poliomyelitis may present a symptomatology of sudden onset of paralysis, stiff neck, fever, and mild pleocytosis in the spinal fluid. Intraspinal tumors are among the conditions which may produce such a picture. Ingraham[1] found five children originally diagnosed as anterior poliomyelitis among sixteen cases of intraspinal tumors in infancy and childhood. Buchanan[2] observed that almost all infants with spinal tumors were first labeled polio or amyotonia congenita.

Spinal tumors are not rare in children according to Grinker and Buey.[3] It may be that many still go undiagnosed by the fact that their symptoms resemble those of other diseases. Many are benign, and even among those tumors not generally so considered, operation may give long periods of relief or possibly cure.[4]

Instances of sudden onset of symptoms with intraspinal tumor have been reported both in adults and children. That this may be the case in metastatic tumor in older age groups is well known. However, that it may also occur in connection with benign tumors may be surprising to those unfamiliar with this field. Naffziger and Brown[5] report a man, aged 42 years, whose first symptom, pain, began abruptly when doing heavy lifting. He was found to have a neurofibroma. Sudden onset with paralysis is more characteristic of children. These authors also report a boy 7 years of age whose flaccid paraplegia came on in two days, and who turned out to have a hemangio-endothelioma. Ingraham[1] writes of a child ten years ten months of age in whom weakness and ataxia of the right hand and arm came on in a period of two weeks. She had an intraspinal meningioma. He reports another patient aged 5 years, sent in by the Infantile Paralysis Commission, and having undergone an orthopedic operation to correct her "contracture," in whom a meningioma was discovered. Another, 13 months old, with inability to hold up her head for four weeks and diagnosed as polio, was found to have a neurofibroma. Six of Ingraham's[1] sixteen patients had neurofibromas, meningiomas, or cholesteatomas.

In three of Ingraham's[1] patients, as well as our own, stiff neck was present. It was not necessary that the tumor be located in the cervical region.

Both Naffziger and Brown[5] and Ingraham[1] report cases with fever, probably related to the tumor. As in our case, fever appeared to be associated with fairly rapid onset of symptoms. It was not confined to tumors of the cervical region where interference with the spinal cord is known to be accompanied by fever.

Two of Ingraham's[1] patients as well as one of our own showed an increase

of white blood cells in the spinal fluid. One of Ingraham's[1] patients had 31 white blood cells per cubic millimeter of spinal fluid, and the other 1,200 white blood cells.

The first patient presented in our series had all of the above findings; sudden onset of paralysis, fever, stiff neck, and pleocytosis. Unfortunately, it did not turn out to be a benign tumor.

Fig. 1 (Case 1).—Unusually dense vertebral body in the neighborhood of the tumor.

CASE REPORTS

CASE 1.—This 2-year-old Negro female was admitted to the Northern Indiana Childrens Hospital on July 7, 1951, because of difficulty in walking and a slight fever. The child had been restless and somewhat nervous for the past two weeks. On July 2, 1951, six days before admission, she complained of stiffness and pain in the legs. A temperature of 101.6° F. was found, and the child vomited several times. She was referred into the hospital as a possible polio. Her mother stated that on July 2, 1951, after a good night's sleep the night before, she got out of bed and found she could not stand. She had been constipated for two weeks.

On admission, stiffness of the neck and spine, weakness of the lower extremities, and active knee jerks were noted. The spinal tap showed 20 white blood cells, 100 per cent polymorphonuclears; protein was 304 mg. per cent; sugar was 80 mg. per cent. A diagnosis of acute anterior poliomyelitis was made. The next day there was marked nuchal rigidity and tenderness of the left calf and thigh. Hot packs were ordered to the neck,

back, and lower extremities and the pain improved. A mass of about the size of a half dollar was noted to the right of the dorsal lumbar spine; it was firm and slightly movable and not tender to palpation. On August 2, almost one month after the onset, there was complete flaccid paralysis of both lower extremities.

Fig. 2 (Case 1).—Complete block shown on myelogram.

X-rays of the spine taken on July 16, 1951, showed marked increase in the density of the eleventh dorsal vertebra. The pedicles of the tenth and eleventh dorsal vertebrae on the left appeared very indistinct.

A repeat spinal tap was not done until Sept. 7, 1951, at which time the leukocytes were 6, protein was 1,835 mg. per cent, and the fluid xanthochromic. It was at this juncture that a neurosurgical consultation was called. A definite sensory level bilaterally at about the tenth dorsal vertebra was noted. A myelogram was ordered but because of technical difficulties was not completed until September 21, at which time a complete block at the level of the second lumbar vertebra was demonstrated.

In summary, this is a case of a 2-year-old girl who suffered from premonitory symptoms for a period of two weeks and awoke one morning with marked weakness of the legs, stiffness of the neck and spine. This soon progressed to complete paralysis of both lower extremities and urinary incontinence. The spinal taps revealed an increasing spinal fluid protein which finally reached 4,000 mg. per cent two months later. Neurological examination showed a sensory level at the tenth dorsal vertebra, and a myelogram revealed an intraspinal space-taking lesion.

CASE 2.—This 4-year-old white female was admitted to the Northern Indiana Childrens Hospital on Oct. 10, 1951, because the left arm hurt and the neck was pulled over to one side. Fever was present. Almost at the same time the neck began to pain her, and she persisted in holding it to the right. Examination revealed nuchal rigidity, slight spasticity of hamstrings and of back musculature. The left arm was weak in biceps and grip. The diagnosis was mild polio. At this time the spinal fluid showed no cells, total protein was 45 mg. per cent, and the sugar was 63 mg. per cent. Treatment consisting of hot packs was applied.

Fig. 3 (Case 2).—Wry neck and fullness at the base.

Fig. 4 (Case 2).—Erosion of the lamina.

On October 19, a note stated that there had been considerable improvement in the function of the affected muscles; a tendency to "curvature of the spine" was noted.

Consultations by an orthopedist, a pediatrician, and a general surgeon finally resulted in a tentative diagnosis of Guillain-Barré. The total protein of the spinal fluid on October 27 was 316 mg. per cent, and there were no cells.

Because of the wry neck, a head halter traction was applied. On November 2, the left arm had become almost completely flail. Retropharyngeal abscess was considered, and was suggested by the x-ray department. This opinion was withdrawn the next day. No mention was made of erosion of the cervical vertebrae.

On November 29, fifty days after admission, the orthopedist suggested that a mass at the root of the neck might represent a neoplasm.

Examination now showed tenderness at the root of the neck with persistent deviation of the head to the right, and a small soft mass, the size of a walnut, close to the cervical vertebrae on the left. The left arm was flaccid, and deep tendon reflexes were absent.

The left lower extremity was spastic, with hyperactive reflexes, ankle clonus, and Babinski sign present. The right lower extremity was quite weak, but not spastic. Meanwhile, the spinal fluid protein had remained elevated.

Fig. 5 (Case 3).—Destructive process involving anterior margins of the tenth to twelfth dorsal vertebrae and intervening discs. Bony bridging.

Now, for the first time, x-ray reported a destructive process involving the sixth and seventh cervical vertebrae on the left.

At this time a neurosurgeon was called, a myelogram ordered, and a laminectomy undertaken. Following the operation the child again began

to move both legs well, and her arms gradually gained strength.

CASE 3.—A 2-year-old Negro child exhibited a sudden onset of paraplegia with no antecedent febrile illness. The child suddenly fell, unable to walk. Initially, there was stiffness of the neck.

Examination two weeks after onset revealed weakness of both legs distal to the knees, and bladder dysfunction. Her findings in general were "consistent with lower motor neuron disease," and a diagnosis of poliomyelitis was made. There apparently was no sensory deficit.

On admission to the Northern Indiana Childrens Hospital, the examiner noted moderate equinus of both feet, "relaxed" hamstring muscles, painful reflex spasm of the back, and knee jerk absent on the right and weak on the left. Ankle clonus was present on the left, and sustained on the right. There was weakness of the quadriceps and toe flexors bilaterally.

X-ray showed a destructive process involving the anterior margins of the eleventh and twelfth dorsal vertebrae and of the anterior portion of the disc between these vertebrae. Similar changes existed between the tenth and eleventh. There was distinct bony bridging over the anterior margins of the vertebral bodies.

The laboratory reported a spinal fluid cell count of zero, total protein of 76 mg. per cent, and chloride of 600 mg. per cent. The Mantoux test was negative.

The chest x-ray was reported negative.

Tubercular and pyogenic abscesses were considered.

Approximately forty days after the first x-ray report, laminectomy was undertaken by another surgeon. An angioma in the extradural space, extending forward between the vertebral bodies, was reported.

COMMENT

That the differential diagnosis between anterior poliomyelitis and spinal cord tumor may be difficult is well demonstrated by these cases. It must be borne in mind that intraspinal tumor can give a picture simulating polio and one must approach the diagnosis considering what is characteristic of each disease, and not merely what may be possible. A spinal fluid protein of over 300 mg. per cent may be possible in polio, but it is not characteristic. Some sensory changes may, temporarily, be possible in polio, but they are unusual. On the other hand, both of these findings are characteristic of intraspinal tumor.

SUMMARY

1. Sudden paralysis, fever, stiff neck, and increased spinal fluid cell count may occur in intraspinal tumor in childhood, as well as in anterior poliomyelitis.

2. Reports of such cases from the literature are reviewed, with the addition of three cases from the Northern Indiana Childrens Hospital.

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THE OPTIMUM DOSE OF POLLEN IN THE TREATMENT OF POLLINOSIS OF CHILDREN

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CONSIDERABLE difference of opinion exists as to what constitutes the optimum dose of pollen in the treatment of pollinosis. There is little disagreement among allergists on the question of coseasonal treatment when a patient presents himself for treatment for the first time during a pollen season. Most are in accord with the principle of very low dosage given intradermally for coseasonal relief. This method, advocated by Phillips[1, 2] and adopted with variations by others including Hansel[3] and Rinkel,[4] has been very effective in our hands. The method consists of giving small doses of pollen extract intradermally at one- to three-day intervals. We administer for coseasonal treatment from 0.01 to 0.1 c.c. of the 1:10,000 dilution (100 units per cubic centimeter, 0.01 = 1 unit)* given intracutaneously at one- to three-day intervals. This dosage is raised or lowered depending on the size of the skin reaction and the clinical results. Our best results seem to occur when the resultant wheal is about the size of a dime, not including the surrounding erythema.

No such general agreement as to dosage exists in regard to preseasonal and perennial treatment of pollen cases. G. T. Brown,[5, 6] among those advocating high dose treatment, recommends amounts in adults up to 100,000 units and proportional amounts in children. At the other end of the scale, among those advocating low dose treatment, one finds Ratner[7] in discussing hay fever treatment in children, recently advising that it is rarely necessary to go higher than 0.1 to 0.3 c.c. of 1:5,000 dilution (20 to 60 units). He "marvels at the audacity" of many allergists who advocate doses up to 1:100 dilutions (10,000 units per cubic centimeter). Among some of those who recommend such "high" top doses for cases of average sensitivity are:

G. T. Brown,[5-6] 60,000 to 100,000 units.
L. Tuft,[8] 10,000 units.
W. T. Vaughan,[9] 20,000 units.
G. L. Walbott and M. S. Ascher,[10] 15,000 units.
S. J. Levin,[11] 30,000 to 60,000 units.
R. A. Cooke,[12] 10,000 to 20,000 units.

These are the recommended top doses for adults. Dosages advised for children are generally proportionately lower, but in Peshkin's[20] experience and in the opinion of most allergists, children tolerate higher pollen dosages in proportion to body weight better than do adults.

"Good results" depend to some extent upon the locality in which allergy

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*The unit referred to in this paper is the Noon unit based on the weight-volume method of pollen extraction which is the simplest method of preparing a reliable pollen extract. One gram of untreated, raw, dry, clean pollen is extracted in 100 c.c. of extracting fluid. This yields approximately 0.1 mg. total nitrogen per cubic centimeter and is arbitrarily labelled as containing 10,000 Noon units per cubic centimeter. In actual practice we make our extracts in 3 per cent concentration, i.e., 3 Gm. per 100 c.c. containing 30,000 units per cubic centimeter and make dilutions from this concentrate. Table I indicates the relationship between this unit and other commonly used methods of labelling extracts.

is being practiced. Undoubtedly those who treat hay fever on the Eastern seaboard can achieve good results with smaller doses due to the lower pollen count generally prevalent in that area, as compared to the Midwest where the pollen count is very often extremely high. Low dosage in the hands of most allergists in the Midwest has not been effective except as a co-seasonal method.

RELATIONSHIP OF SKIN TEST SENSITIVITY TO TOP DOSAGE

Generalizations are inaccurate in discussing pollen dosage in relation to skin test sensitivity. Usually, however, the higher the degree of skin sensitivity, the lower the top dosage necessary to produce good results. The chief contribution of the low-dosage advocates is that they have emphasized again that a small percentage of cases cannot tolerate high dosage but, on the contrary, this type of case can be made worse. There is, however, no easy way to diagnose such cases in advance of treatment. Quantitative skin tests by the method of serial dilution intradermally[13] do not help enough in our experience in either adults or children to make this method worth doing as a routine procedure. We make no attempt to rigidly classify our cases according to this method as A, B, C, or D degrees of sensitivity. On the contrary, we agree with Peshkin's[14, 20] contention that this commonly practiced procedure should be eliminated from allergic practice.

We have adopted a very simple procedure which for practical purposes indicates sufficiently accurately the degree of *skin* sensitivity. This is to make scratch tests using a scarifier producing uniform scratches, one such as that suggested by Lewis Webb Hill.[15] Three per cent pollen extracts are applied to the scratches which are carried out as uniformly as possible in all patients. The size of the resultant skin reaction indicates the degree of *skin* sensitivity and *roughly* the clinical sensitivity. A small percentage of typical pollen cases does not react at all by scratch testing. In these cases if the scratch test reaction is questionable, we follow the scratch test by 0.02 c.c. of the 1:100 dilution (200 units) intradermally. Should this test be negative, we then make an intradermal test with 0.02 c.c. of the 1:33 dilution (600 units.). We do not hesitate to follow a totally negative scratch test with the 1:33 dilution (3 per cent extract), omitting the 1:100 dilution in such cases. Rarely, in children, does one find pollen-sensitive patients not reacting to the 3 per cent extract intradermally. However, skin-test negative patients can be tested subsequently by the ophthalmic or intranasal method. Some of the patients who fail to react except to the 3 per cent intradermal test do not tolerate as high a top dose of pollen as some of those who react to scratch

TABLE I. COMPARISON OF METHODS OF LABELLING POLLEN EXTRACTS

DILUTION WT./VOL.	PER CENT	NOON UNITS PER C.C.	TOTAL NITROGEN MG. PER C.C.	PROTEIN NITROGEN UNITS PER C.C.
1:10,000	0.01	100	0.001	64
1: 1,000	0.1	1,000	0.01	640
1: 100	1.0	10,000	0.1	6,400

100 protein nitrogen units = approximately 150 Noon units.

tests. These variations in ability to tolerate high pollen dosages not related to skin test sensitivity can be discovered only by the development of excessive local or occasionally constitutional reactions which may occur when least expected in these cases.

DOSAGE AND METHOD OF PRESEASONAL AND PERENNIAL THERAPY

Our experience with many hundreds of pollen-sensitive children (hay fever and/or asthma), in both private practice and in the Allergy Clinic of the Children's Hospital, does not bear out the claim that low-dose therapy is as effective as our methods presently in use. We concur with Rockwell's frequently quoted opinion (quoted more recently by Abramson[16]) that the maximum tolerated dose is the one which gives the best results, and, in general, the higher the dose, the better will be the clinical results. The average child with pollinosis can tolerate approximately 0.5 to 1 c.c. of the 1:33 dilution, equivalent to 15,000 to 30,000 units, depending on the age of the child. This supposedly high dosage is easily achieved in approximately twenty-five injections in the child with average sensitivity (Table II) and is what we consider the optimum dosage to achieve best results. Younger children are given 15,000 units top dose and a considerable number of older children are given up to 1 c.c. (30,000 units) without encountering difficulty. The top dose should be reached just prior to the pollinating season. This amount is then continued at weekly intervals during the season, giving at this time a small part of each injection intracutaneously. At the end of the pollen season, the dosage is cut by 50 per cent ("the maintenance dose") and con-

TABLE II. APPROXIMATE SCHEDULE OF DOSES FOR POLLEN INJECTIONS

DOSE	NOON UNITS	C.C.	BOTTLE	UNITS PER C.C.	DILUTION WT./VOL.
1st	5	0.05	No. 1	100	1:10,000
2nd	10	0.1			
3rd	20	0.2			
4th	35	0.35			
5th	60	0.6			
6th	100	0.1	No. 2	1,000	1:1,000
7th	150	0.15			
8th	250	0.25			
9th	400	0.4			
10th	650	0.65			
11th	1,000	0.1	No. 3	10,000	1:100
12th	1,500	0.15			
13th	2,000	0.2			
14th	3,000	0.3			
15th	4,000	0.4			
16th	5,000	0.5			
17th	6,500	0.65			
18th	8,000	0.8			
19th	9,000	0.3	No. 4	30,000	1:33 (3%)
20th	10,500	0.35			
21st	13,500	0.45			
22nd	16,500	0.55			
23rd	21,000	0.7			
24th	25,500	0.85			
25th	30,000	1.0			

This schedule is approximate for cases of average sensitivity. Initial and top doses will be lower for more sensitive patients.

tinued every three weeks until six or seven weeks prior to the next pollinating season. It then requires but six to eight weekly injections, increasing the dosage each time, as per the schedule (Table II), to bring the dosage back to the previous top level. A small percentage of patients is unable to tolerate the top dosage during the pollinating season. Should there be any tendency to aggravation of symptoms following a pollen injection during the season, the dosage should be cut by 50 per cent, or more if necessary.

RESULTS

Our experience with high-dose treatment is that most children can be given 80 to 90 per cent relief the first season of treatment (grass or weed pollen) and can stop treatment permanently in 50 per cent of cases in from three to five years of continuous perennial high-dose therapy. The development of asthma in patients thoroughly treated rarely occurs. Asthma already present generally clears up as readily or sooner than the hay fever symptoms.

LOCAL REACTIONS

The local reaction remains one of the best guides to increase in dosage provided the several factors involved in the production of local reactions are considered. Among the most important cause of local reaction is the use of pollen extracts containing 50 per cent glycerin as a preservative. Severe local reactions, accompanied by considerable pain and tenderness, result when sizeable volumes of glycerinated extract are given subcutaneously. For this reason, because we use fairly large volumes of pollen extracts (0.5 to 1 c.c.) in children, and even larger volumes in adults as our top dosage, we have discontinued the use of glycerinated extracts for many years. We use pollen extracts prepared in a nonirritating alkaline 5 per cent dextrose solution as evolved by Unger and Moore.[17] Another cause of excessive local reaction is the deposition of the pollen extract too close to the surface of the skin. As pointed out many years ago by Thommen,[18] the skin being the most reactive of the superficial tissues, the closer the injection is to the surface, the greater the reaction. We have proved this point many times by administering a dose on one occasion superficially and the same dose on another occasion intramuscularly, with a severe local reaction in one case and practically no local reaction in the latter instance. Absorption of pollen extract has been shown[19] to be appreciably slower when given intramuscularly than when given subcutaneously. For this reason, because of slower absorption and because of smaller local reactions when given deeply, we administer all pollen injections intramuscularly except for a small amount of each injection given intracutaneously during the pollen seasons. It goes without saying that an additional cause of excessive local reaction is too rapid an increase in dosage, which should be guarded against. When injections are given deeply with nonglycerinated solutions as outlined above, local reactions of any consequence very rarely occur, with proper increase of dosage.

GENERAL REACTIONS

The advocates of small pollen dosage claim as one of the advantages of their method the almost complete absence of general (constitutional) reactions. Our experience in using high-dose treatment is very much the same as reported

by others, that the tendency to reactions occurs at the lower dosage levels, apparently before some degree of immunity is established. General reactions at the higher levels are extremely rare provided, of course, proper precautions are taken as to vascular puncture. During the past five years, over 15,000 pollen injections have been administered in our clinic patients. During this period of time, epinephrine injections to overcome a constitutional reaction following pollen treatment have been administered eight times, or at the rate of about one reaction per two thousand injections. General reactions in our private practice have occurred about as rarely. The infrequency of systemic reactions in our practice has not been the result of including in each injection a small dose of epinephrine as others have advocated. We cannot condemn too strongly the practice of routinely including small amounts of epinephrine in pollen injections as a method of avoiding reactions. Many children develop extreme pallor, nausea, and even shocklike symptoms as a result of even small epinephrine injections when given in the absence of allergic symptoms. For this reason, in order to avoid reactions in those patients exhibiting extreme sensitivity, we prefer to incorporate in each pollen injection administered to such patients a small amount of an antihistaminic (0.25 to 0.5 c.c. Decapryn = 1.25 to 2.5 mg.). Other antihistaminics in parenteral solution are also effective and very useful for this purpose.

It is not within the scope of this paper to discuss other measures of great value as adjuncts in the treatment of pollinosis. These include the use of sympathomimetic drugs, the antihistaminics orally, and proper medication for the eyes, nose, and lower respiratory tract when indicated. In addition, concomitant sensitivities may require uncovering and elimination and/or desensitization (immunization). "Good results" are dependent to some extent on the thoroughness with which these additional measures are carried out. Such details can be found in most standard texts on allergy.

SUMMARY

1. The maximum tolerated dose is the optimum dose for the pollen-sensitive patient (Rockwell).

2. Coseasonal treatment for a patient not previously treated is best carried out by means of small intradermal injections at one- to three-day intervals.

3. Small-dose therapy has not been as effective in our hands as high-dose therapy for preseasonal and perennial desensitization (immunization).

4. Children tolerate high-pollen dosage at least as well if not better than do adults.

5. For the child of average sensitivity 0.5 to 1 c.c. of 3 per cent pollen extract (15,000 to 30,000 Noon units) is the optimum dosage.

6. In general, the greater the degree of skin sensitivity to pollen tests, the smaller the top dosage of pollen extract required. There are many exceptions to this generalization. Quantitative skin tests by the serial dilution method are not accurate enough to predict top dosage, and are therefore not advisable as a routine procedure.

7. The best guide to pollen dosage is the local reaction, provided important factors other than dosage are considered. These are (a) depth of injection,

and (b) irritation due to the extracting fluid used.

8. General reactions occurred with relative infrequency, despite the high doses used in hundreds of pollen-sensitive children, provided increase in dosage and other precautions are properly carried out.

9. The results of high dose therapy in pollen-sensitive children have been excellent. Eighty per cent of our patients receive excellent results the first year of such preseasonal therapy. Fifty per cent can discontinue treatment in from three to five years of continuous preseasonal and perennial therapy when treatment is carried out according to the method outlined.

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REDUCTION OF MORTALITY IN THE PREMATURE NURSERY

II. Incidence and Causes of Prematurity: Ethnic, Socioeconomic and Obstetric Factors

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THE New York State Department of Health,[1] in a study of infant mortality by hospitals in New York State exclusive of New York City for the period of 1945 to 1949, reported 684,665 live births of which 45,546 were prematures. They showed that the premature neonatal mortality rate was ten times the rate among full-term infants, and that these infants accounted for 63.9 per cent of all neonatal deaths.

In a preceding paper,[2] we demonstrated the declining role of infection as a major cause of neonatal deaths in the modern premature nursery. We concluded that the principal obstacles to reduction of fatalities are:

1. The great loss of infants born in the low weight groups. (In contrast, an insignificant loss in the upper weight groups.)
2. The short survival period of less than twenty-four hours in 60 per cent and less than one week in 95 per cent of fatal cases. (This situation permits only a limited time for application of supportive measures.)
3. The inadequacy of available means to successfully sustain life and speed up the process of growth and development of most premature infants born in the fatal low weight groups to a level of maturity essential for life.

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It is obvious that prevention of premature birth in the low weight groups would favorably alter the large contribution of prematurity to neonatal mortality. However, to achieve successful prevention of premature labor requires more enlightenment on the several causes of prematurity and their relative importance. Studies of the incidence of prematurity under varying maternal conditions should reveal some significant aspects of its etiology.

With these thoughts in mind, we undertook to evaluate the influence of ethnic origin, the socioeconomic status and obstetric complications of the pregnant mother on the occurrence of premature labor.

METHOD OF STUDY

The Beth-El Hospital, Brooklyn, a semiprivate institution, where approximately 3,500 mothers are delivered annually, offered us the major source of material for study.

Our cases were analyzed for the following data:

1. The incidence of premature births in ward and private patients.
2. The incidence in Negro and white patients, ward and private.
3. Maternal and obstetrical conditions associated with premature labor.

The Kings County Hospital, Brooklyn, a city institution, which admits patients only from the lower economic

groups, offered the opportunity to investigate the incidence of prematurity based on ethnic origin among a large group of patients with almost similar environmental and socioeconomic backgrounds.

all deliveries at the Beth-El Hospital, the incidence was 12 per cent for ward patients, and only 8.6 per cent for private patients. At the Kings County Hospital, the incidence was 15.3 per cent.

TABLE I. INCIDENCE OF PREMATURITY BASED ON ECONOMIC STATUS

	BETH-EL HOSPITAL			KINGS COUNTY HOSPITAL
	TOTAL	PRIVATE	WARD	
No. of obstetric cases	11,170	9,925	1,245	7,641
No. of full-term newborn infants	10,170	9,073	1,097	6,469
No. of premature newborn infants	1,000	852	148	1,172
Per cent full-term newborn infants	91	91.4	88	84.7
Per cent premature newborn infants	9	8.6	12	15.3

TABLE II. INCIDENCE OF PREMATURITY BASED ON ETHNIC ORIGIN AND ECONOMIC STATUS

	BETH-EL HOSPITAL				KINGS COUNTY HOSPITAL	
	WHITE		NEGRO			
	PRIVATE	WARD	PRIVATE	WARD	WHITE	NEGRO
No. of obstetric cases	6,566	525	116	310	2,283	5,358
No. of full-term newborn infants	6,004	467	104	264	1,998	4,471
No. of premature newborn infants	562	58	12	46	285	887
Per cent full-term births	91.5	89	90	85	87.5	83.5
Per cent premature births	8.5	11	10	15	12.5	16.5

TABLE III. CONDITIONS ASSOCIATED WITH PREMATURE BIRTHS AT THE BETH-EL HOSPITAL

	WHITE			NEGRO		
NUMBER OF PREMATURE BIRTHS	PRIVATE 805	WARD 77	TOTAL 882	PRIVATE 16	WARD 62	TOTAL 78
1. Multiple pregnancy	63	7	70	0	[illegible]	4
2. Breech presentation	53	5	58	0	[illegible]	0
3. Bleeding during pregnancy	11	0	11	0	[illegible]	1
4. Maternal illness	11	5	16	1	[illegible]	2
5. Congenital anomalies	7	0	7	0	1	1
6. Toxemia	54	7	61	0	6	6
7. Placenta previa	30	4	34	0	0	0
8. Premature separation of placenta	26	4	30	0	3	3
9. Repeat cesarean section	16	0	16	2	2	4
10. Rising Rh titer	1	0	1	0	0	0
Number with associated conditions	272	32	304	3	18	21
Number without associated conditions	533	45	578	13	44	57
Per cent with associated conditions			34			27
Per cent without associated conditions			66			73

OBSERVATIONS

Our results are presented in three tables.

Table I shows the influence of the maternal socioeconomic status on the incidence of prematurity. While premature birth occurred in 9 per cent of

Table II compares the premature incidence in Negro and white mothers of different socioeconomic levels. At the Beth-El Hospital, white private patients had a premature incidence of 8.5 per cent compared to 11 per cent for white ward patients. Negro ward pa-

tients had an incidence of 15 per cent, whereas Negro private patients had only 10 per cent. At the Kings County Hospital, the premature incidence for Negro mothers was 16.5 per cent compared with 12.5 per cent for white mothers.

Table III notes the maternal and obstetrical conditions associated with premature births at the Beth-El Hospital. A total of 960 successive premature births were studied. In only 325 was an associated condition present. Maternal illness, such as tuberculosis, diabetes, pneumonia, and syphilis, accounted for 18; induced therapeutic premature delivery, in cases of toxemia, placenta previa, premature separation of the placenta, repeat cesarean section, and a rising Rh titer, accounted for 155; and the remainder, 152, were principally multiple pregnancies and breech presentations. Thus 68 per cent of all premature births occurred spontaneously without any evident maternal or obstetrical condition; 16 per cent were associated with multiple pregnancy and breech presentations; and 16 per cent with induced premature birth.

DISCUSSION

Dunham[3] estimated that 5 per cent of approximately three million births in the United States were premature. Many theories have been advanced to explain the accident of premature birth.

Bain and associates[4] reported regional variations. They found that the incidence of prematurity was higher in the South; and concluded that skin color determined sectional differences.

Ethnic origin as a cause of prematurity was given support by Brown and associates.[5] The concept that curly hair, brown eyes, and a broad nose in a pregnant mother dictates the state of maturity of her newborn infant requires scientific substantiation. Certain facts concerning the Negro people in the United States are indisputable. They have less income, more illness, a lower social and economic position, and inferior housing. Negro mothers give birth to more premature infants, to a large number in the low weight groups, and sustain a greater loss of newborn infants.[3, 4, 6, 7] The Statistical Bulletin[8] of the Metropolitan Life Insurance Company reported that: "In the United States as a whole, the neonatal mortality among the nonwhite is higher by nearly 40 per cent. In the first three days the excess mortality is about 25 per cent, while in the remainder of the month, when environmental factors play a greater role, the rate is nearly 80 per cent higher than the white babies." It is a greater likelihood, therefore, that maternal nutrition and socioeconomic circumstances, factors which so largely influence nonwhite neonatal mortality, determine the state of maturity of the nonwhite newborn infant. Our studies supported this impression. We found that the incidence of premature births in the Negro mother was high—15 and 16.5 per cent, respectively, in the Beth-El Hospital ward and at the Kings County Hospital. But with improvement in the economic status, as evident in private Negro patients, a drop in the incidence of prematurity from 15 to 10 per cent was observed.

The equal and relentless effect of maternal nutrition and socioeconomic conditions on newborn maturity, irrespective of color, was shown by the higher incidence of prematurity in all ward patients—12 per cent at the

Beth-El Hospital and 15.3 per cent at the Kings County Hospital compared with 8.6 per cent for private patients at the Beth-El Hospital. Frequent observations have been made to support the theory that newborn maturity depends on maternal nutrition and socioeconomic circumstances. It was shown in Holland, Greece, and Russia during World War II that starvation resulted in prematurity, abortions, and stillbirths. Ratner and associates[9] noted that the incidence of premature birth in tuberculous mothers was 23 to 64 per cent depending on their nutritional status. A hospital[10] with a preponderant private obstetric service reported an incidence of 7.9 per cent; whereas, a public institution in the same city reported[6] an incidence of 15.5 per cent. A Children's Bureau study[3] credited ward patients with a higher incidence. Eastman[7] observed that premature delivery occurred more frequently in Negro ward patients. Tompkins[11] noticed a definite association between adequate nutrition in the mother and premature labor. Monerieff[12] found that a steep rise in premature birth occurred as the economic level decreased.

The influence of accidents, chronic disorders, and maternal infections on the incidence, cause, and prevention of premature birth is questionable.[13] Obstetric complications play but a minor role.[7, 14, 15] Eastman[16] demonstrated that approximately 70 per cent of premature labors were of spontaneous onset, in single pregnancies and without known cause. Our observations in Table III fully substantiated these reports. We found that maternal illness, such as diabetes, pneumonia, syphilis, and tuberculosis, played a negligible role in premature labors, and, most likely, exerted its greatest influence on the nutritional status of the mother. We observed that, of the 960 premature births reported in Table III, 16 per cent were associated with induced therapeutic premature delivery because of toxemia, premature separation of the placenta, placenta previa, repeat cesarean section, and a rising Rh titer; 16 per cent were associated with multiple pregnancies and breech presentation; and 68 per cent occurred spontaneously without any evident maternal or obstetrical condition. In this latter group, the factor which probably contributed most to precipitating premature labor was the nutritional status of the mother determined by the socioeconomic condition of her environment or by faulty nutritional habits.

CONCLUSION

1. Of the three maternal conditions selected for investigation, the socioeconomic status of the pregnant mother was found to be a major influence in determining maturity of her newborn infant. A significant increase in the incidence of prematurity was found in ward patients as compared with private patients.

2. Ethnic origin played no part in determining newborn maturity. Socioeconomic factors affected white and Negro mothers alike.

3. Maternal illness had a negligible effect on the incidence of premature birth. Its influence was felt most likely on the condition of maternal nutrition.

4. Obstetric conditions were linked with 32 per cent of premature births. Of 960 premature births, 16 per cent were associated with induced therapeutic premature delivery because of toxemia, placenta previa, premature separation of placenta, repeat cesarean

section, and a rising Rh titer; 16 per cent were associated with multiple pregnancies and breech presentation; and 68 per cent occurred spontaneously without any evident maternal or obstetrical condition.

5. The occurrence of premature birth is primarily a public health problem concerned basically with the socioeconomic status and nutritional condition of the pregnant mother. Inadequately prepared for the nourishment of the fetus, the pregnant mother more often delivers prematurely.

Acknowledgment is made to Dr. George E. Brockway, consultant pediatrician to the Kings County Hospital, for permission to use some of the statistics included in Tables I and II; and to Drs. Howard Scalettar, Rudolph Ginattasio, and Michael Prizzo of the Kings County Hospital resident staff for assistance in these investigations.

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FURTHER STUDIES IN CONGENITAL CRANIAL OSTEOPOROSIS (CRANIOTABES)

II. Its Relationship to Cranial Molding and Duration of Labor

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THIS study is one of a series[2, 3, 3a, 21] dealing with the etiology and significance of congenital cranial osteoporosis, known also as congenital craniotabes.* Based on 1,425 newborn infants in Los Angeles and Mexico City, it presents additional observations on the relationship of congenital craniotabes to cranial molding and duration of labor.

Further knowledge about the molding mechanism in relation to cranial osteoporosis may be of practical obstetric as well as pediatric interest. For example, the danger of intracranial birth hemorrhage due to excessive molding is greater in premature infants because of the increased plasticity or compressibility of their incompletely calcified, osteoporotic skulls.[10, 14, 20, 23] Thus, the question arises whether congenital cranial osteoporosis might not also be a factor predisposing to intracranial birth trauma in the full-term infant.

For the following reasons this question is practical rather than merely academic: (1) The degree of calcification of the infant's skull at birth may be influenced by prenatal measures, such as maternal exposure to sun,[3, 21] or supplemental administration of dicalcium phosphate with vitamin D.[5, 12] (2) Such prenatal therapy has become almost universal in obstetric practice, although whether it is beneficial or detrimental from the standpoint of intracranial birth trauma has not been settled.

NATURE AND SCOPE

The earlier study[21] has been supplemented by additional observations on the incidence of congenital craniotabes in relation to cranial molding and separation of cranial sutures in the infant, the type of delivery, whether spontaneous or instrumental, and average duration of labor.

The relation of cranial molding to the size of the infant's head and the relation of average duration of labor to the size of the infant's head and maternal parity were also studied.

MATERIAL AND METHODS OF INVESTIGATION

A new series of seventy-five infants, obtained as in the earlier investigation from the obstetric wards of the Los Angeles County General Hospital, brought the total number of infants in the Los Angeles series to 875.

Additional observations on cranial molding and separated cranial sutures in a new series of 550 infants from the obstetric wards of two municipal hospitals in Mexico City ("Hospital

From the Department of Pediatrics of the University of Southern California School of Medicine and the Los Angeles County General Hospital, through a grant from Mead Johnson and Company.

*The term "congenital craniotabes" is used in this paper as a descriptive clinical term for congenital softness of the skull in the newborn infant, whereas the term "congenital cranial osteoporosis" is used in reference to its underlying pathology.[2]

General" and "Maternidad de las Lomas") were obtained in the summers of 1941 and 1942. Thus the total number of infants in the combined Los Angeles and Mexico City series was 1,425.

The data pertaining to the duration of labor and type of delivery were furnished by the records of the Los Angeles County General Hospital.

The type of material, methods of investigation, and criteria for the classification of infants into the various skull-type categories are essentially the same as in the earlier reports.[2, 21]

Briefly, infants were arbitrarily classified into three groups: (1) infants with "hard" skulls showed no yielding or compressibility of bone on light or moderate palpation; (2) those with "soft" skulls showed a definite yielding or softness (either "ping-pong" or "parchment" in type) of more than one-half the bony vertex; and (3) those with "transitional" skulls showed all lesser degrees of bony softness no matter how small the area of involvement. The soft skull group with the marked form of cranial softness, and the transitional with the slight or moderate forms, together constitute the "osteoporotic" skull group.

The contention that such classification based wholly upon clinical diagnostic criteria must be arbitrary is admitted. Nevertheless, it is as accurate and objective as is possible in a purely clinical investigation, since craniotabes can be much better appreciated by palpation than by roentgenographic visualization.[6]

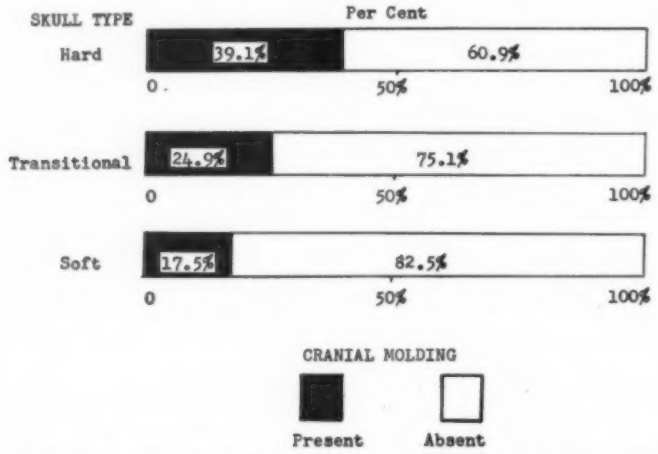

Fig. 1.—Incidence of cranial molding among infants with hard and osteoporotic skulls.

RESULTS OF THE INVESTIGATION*

As in the previous studies, the reliability of the results obtained was determined by applying the critical ratio and the Chi square tests.[2]

1. Cranial Molding.—Cranial molding is generally regarded as being of two types: (1) molding by overriding of sutures, and (2) molding by plastic deformation.[9, 28] As in the earlier investigation[21] the sole criterion for cranial molding was overriding of sutures.

*Numerous tables pertaining to the results of the investigation have been omitted. They may be obtained from the author.

No observations on molding by plastic deformation were attempted since it does not lend itself to reliable evaluation. Thus, molding was considered "present" when definite overriding of sutures was observed and "absent" when the sutures, particularly the sagittal, were either barely approximated or frankly separated.

The earlier results indicated that molding occurred twice as frequently during the neonatal period in infants with hard as with soft skulls (Fig. 1). The difference between the hard and the osteoporotic skull groups was statistically highly significant.[21] Further analysis of the data showed that molding was twice as frequent in infants with hard skulls in both the early and the late neonatal periods.

In this study the incidence of cranial molding was also determined for infants with hard and osteoporotic skulls within the occipitofrontal head circumference groups, designated as "large," "average," and "small," according to the standards previously described.[21] The purpose was to ascertain whether the higher incidence of overriding sutures observed among infants with hard skulls postnatally might not indicate that they are actually subject to more molding because their heads are larger, as is suggested by the larger average head circumference of hard skull infants.[3, 21] Table I shows that molding occurred more frequently in infants with hard skulls in each of the three head circumference groups, a high degree of statistical significance being established for the difference between the hard and the osteoporotic skulls in the total and large head circumference groups (critical ratio values: 3.86 and 4.68, respectively). No consistent relationship was present between the degree of molding and the size of the infant's head (Table I). Thus, the higher incidence of overriding sutures observed postnatally among infants with hard skulls is not due to their larger average head circumference.

The higher incidence of molding by overriding of sutures among the newborn infants with hard skulls was subsequently confirmed in the investigation conducted in Mexico City. In the

TABLE I. DISTRIBUTION OF CRANIAL MOLDING IN RELATION TO SIZE OF THE OCCIPITOFRONTAL HEAD CIRCUMFERENCE AMONG INFANTS WITH HARD AND OSTEOPOROTIC SKULLS

	TOTAL		TYPE OF SKULL							
			HARD		TRANSITIONAL		SOFT		TRANSITIONAL PLUS SOFT	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Size of head circumference										
Large	256	100.0	216	100.0	37	100.0	3	100.0	40	100.0
Molding,										
Present	43	16.8	42	19.4	1	2.7	0	0.0	1	2.5
Absent	213	83.2	174	80.6	36	97.3	3	100.0	39	97.5
Average	323	100.0	210	100.0	85	100.0	28	100.0	113	100.0
Molding,										
Present	175	54.2	122	58.1	42	49.4	11	39.3	53	46.9
Absent	148	45.8	88	41.9	43	50.6	17	60.7	60	53.1
Small	215	100.0	110	100.0	77	100.0	28	100.0	105	100.0
Molding,										
Present	24	11.2	14	12.7	10	13.0	0	0.0	10	9.5
Absent	191	88.8	96	87.3	67	87.0	28	100.0	95	90.5

new series of 548 newborn infants, molding occurred in 54.4 per cent of the 434 infants with hard skulls, 39.0 per cent of the 114 infants with transitional skulls, and 35.7 per cent of the fourteen infants with soft skulls, the difference between the hard and the total osteoporotic skull group being statistically significant (critical ratio: 3.07). In 112 infants in this series who had exceptionally hard and thick cranial bones, the incidence of molding was the highest observed, 68.7 per cent, and the overriding of sutures the most prominent. Thus, molding, as in the Los Angeles series, was twice as frequent in infants with very hard skulls as with soft, the difference having a high degree of statistical significance (critical ratio: 2.48), despite the small number of infants in the soft skull group.

2. Type of Cranial Sutures.—Cranial sutures were arbitrarily classified into three types: (1) separated, (2) approximated, and (3) overriding.[21]

The earlier results indicated that separated sutures occurred in 15.9 per cent of infants with hard skulls, 25 per cent of those with transitional, and 28.8 per cent of those with soft.[21]

The higher incidence of separated sutures among infants with osteoporotic skulls, consistent with the lower incidence of overriding sutures observed among them, was confirmed in the investigation conducted in Mexico City. In the new series of 536 infants, separated sutures occurred in 24.8 per cent of the hard and 39.8 per cent of the osteoporotic skull groups, the difference being significant according to the critical ratio (C.R. value: 2.91) and the Chi square test (P value: 0.01–). In the 112 infants with exceptionally hard and thick cranial bones mentioned above, the incidence of separated cranial sutures was only 15.3 per cent, significantly lower than the 39.8 per cent derived for the total osteoporotic skull group (critical ratio: 4.46).

The more frequent occurrence of widely separated sutures among newborn infants with osteoporotic skulls was also observed by other investigators,[1, 15, 25] but was interpreted as a sign of defective ossification.

3. Type of Delivery and Average Duration of Labor.—Many obstetricians believe that increased bony density of fetal cranial bones, especially in the parietal region, may affect molding adversely.[5, 7, 12] The earlier study of the incidence of instrumental deliveries in relation to congenital craniotabes[21] was therefore supplemented by a determination of the average duration of labor for infants with hard and with osteoporotic skulls, the question being whether a hard or well-calcified skull is more likely to predispose to instrumental delivery or prolonged labor than a soft or osteoporotic and presumably more flexible skull.

Instrumental deliveries were found to occur even less often in infants with hard skulls (15.6 per cent) than in those with osteoporotic skulls (17.1 per cent), although the difference was statistically nonsignificant. These results support the previous conclusion that hard, normally calcified skulls do not predispose to instrumental delivery.

The average duration of labor was based on 312 spontaneous deliveries in the Anglo-American group only, in order to eliminate the possible influence of a racial factor. It was derived for the 80 primiparas and 232 multiparas separately, in relation to the infant's

sex and type of skull. The average duration of labor was 16.7 hours for primiparas and 9.7 hours for multiparas. The average duration of labor is also somewhat higher for male infants: 18.8 hours for the first-born male infants and 10.9 hours for the later born; 15.1 hours for the first-born female infants and 9.3 hours for the later born. The higher average duration of labor for male infants is also found in the hard skull group and in the total (Table II). The only difference, however, which has any degree of statistical significance is that somewhat lower among female infants, but none of the differences observed is statistically significant.

These results indicate that the average duration of labor in spontaneous births is dependent on maternal parity, and to some extent on the size of the infant's skull rather than on the degree of calcification. Finola and his co-workers,[12] as well as Leavenworth,[17] have also reported the absence of an appreciable difference between the average duration of labor for infants with adequate cranial calcification and those with deficient calcification.

TABLE II. AVERAGE DURATION OF LABOR IN RELATION TO INFANT'S SEX AND TYPE OF SKULL

	TOTAL		TYPE OF SKULL							
			HARD		TRANSITIONAL		SOFT		TRANSITIONAL PLUS SOFT	
	NO.	MEAN ± S.D.	NO.	MEAN ± S.D.	NO.	MEAN ± S.D.	NO.	MEAN ± S.D.	NO.	MEAN ± S.D.
Males	155	12.7 ± .970	100	14.0 ± 1.347	36	9.5 ± *	19	11.8 ± *	55	10.3 ± 1.135
Females	157	10.9 ± 1.223	112	10.8 ± .799	38	11.0 ± 1.646	7	12.7 ± *	45	11.3 ± 1.646
Total	312	11.8 ± *	212	12.3 ± .805	74	10.3 ± *	26	12.1 ± *	100	10.7 ± .960

*S.D. not determined.

between the male and the female infants in the hard skull group (critical ratio: 2.04). In the osteoporotic skull group the average duration of labor is slightly higher for the female infants instead of the male, but the difference is statistically nonsignificant.

The higher average duration of labor for male infants is correlated with their larger size at birth. Accordingly, the size of the infant's head is probably a factor in the duration of labor, particularly in primiparas since they showed the greatest difference in the average duration of labor for male and female infants.

No consistent trend in the average duration of labor for infants with hard and with osteoporotic skulls is shown in Table II. The average duration of labor was somewhat higher for the hard skull group among male infants, and

COMMENT

The bearing of congenital cranial osteoporosis upon cranial molding, average duration of labor, and incidence of instrumental deliveries has special interest in connection with the etiology of intracranial birth trauma. *First,* the mechanical effects of the forces of labor upon the fetal head are the immediate cause of traumatic intracranial birth hemorrhage, whatever contributing factors, such as lowered capillary resistence and blood coagulability, may exist.[11, 13, 18, 19, 20, 23] *Second,* the danger of intracranial birth hemorrhage due to excessive molding is far greater in premature infants, since the undue thinness or excessive plasticity of their osteoporotic cranial bones may result in greater molding and deformation of the various diameters of the

fetal head, and lead to tentorial tears and hemorrhage into the brain.[8, 10, 13, 14, 20, 23] *Third,* rapid cranial molding, such as occurs in precipitate labors and breech deliveries,[4, 7, 19a, 20a, 23, 24] as well as rapid springing apart of the parietal bones immediately upon birth,[22, 23] have been implicated as factors in intracranial birth hemorrhage. We are led to question whether osteoporotic cranial bones might not offer less protection to the brain against the forces of labor than well-calcified ones, whether the full-term infant with osteoporotic cranial bones might not be as susceptible to excessive or rapid molding as the premature infant, and, thus, whether congenital cranial osteoporosis might not well be a factor predisposing to intracranial birth trauma in the full-term infant.

A more gradual molding mechanism in infants with hard or well-calcified skulls is suggested by the finding that overriding sutures in the neonatal period were twice as frequent among them as among infants with soft or osteoporotic skulls. Since soft skulls, per se, are not subject to less molding in the process of labor than the hard, the more rapid post-partum return of their sutures to normal may indicate either that they are more resilient, or that they are subject to a different mechanism of molding, i.e., more molding by plastic deformation and less by overriding of sutures. However, even with the same molding mechanism, the widely separated sutures observed more frequently among infants with osteoporotic skulls might also result in less bony overriding, proportionate to the degree of separation, as well as in greater resiliency.

Thus molding may be influenced by the degree of fetal cranial calcification either directly through the degree of bony plasticity, or indirectly through the degree of separation of sutures. Specifically, the soft, osteoporotic skull by virtue of its more widely separated sutures and increased bony plasticity, would be more subject than the well-calcified skull to excessive or rapid molding and rapid springing apart of the parietal bones upon birth, all of which have been implicated as predisposing to intracranial birth hemorrhage.[4, 13, 14, 19a, 20, 20a, 22, 23]

Although the greater flexibility of fetal cranial bones might produce greater ability to mold, neither the average duration of labor in spontaneous births, nor the incidence of instrumental delivery was significantly different among infants with hard and with osteoporotic skulls. A softer, osteoporotic skull, then, does not generally offer any advantage obstetrically, and the possibility that it might offer certain advantages under such abnormal conditions as borderline dystocia or uterine inertia remains purely speculative.

Instead, hard, normally calcified skulls appear to have definite advantage obstetrically over osteoporotic ones, by virtue of their possibly greater protective quality, more gradual molding, and lesser danger of excessive molding. Certainly a well-calcified skull may be considered normal; in this study more than 70 per cent of infants of mothers not receiving supplemental vitamin D during pregnancy had hard skulls and only about 7 per cent had soft or frankly osteoporotic ones.[2, 21]

An abnormally hard or an osteosclerotic skull,[5, 12, 23] however, like an osteoporotic one, might present some danger to the infant from the standpoint of intracranial birth hemorrhage

—the osteoporotic, with its increased ability to mold, through a primarily traumatic mechanism, and the osteosclerotic, with its decreased ability to mold, through a primarily anoxic mechanism. Accordingly, although this study fully supports the current obstetric practice of administering supplemental vitamin D prenatally, the warning against its indiscriminate use in large doses[12] may be justified.

The observed predilection of congenital craniotabes for the parietal bones, since their importance in the process of molding is paramount,[12, 18] highlights the need for investigating the relationship of cranial osteoporosis to intracranial birth trauma in the full-term infant. The need is confirmed by the following evidence in the literature: First, the incidence of both intracranial birth hemorrhage and congenital cranial osteoporosis is greater among male infants[2, 3, 24, 29] and offspring of older primiparas,[1, 2, 21, 24, 26] and second, the geographical and seasonal distribution of both appears to follow inversely the curve of sunshine. Thus, the reported lower mortality rate from intracranial birth hemorrhage in the southern and southwestern United States,[24] and for the summer months,[16] is analogous to the lower incidence of congenital cranial osteoporosis in sunnier localities and in the late spring and summer months.[2, 21] Although the higher incidence of intracranial birth injury in male infants is, of course, partly due to their larger size at birth,[24, 29] the higher incidence in offspring of older primiparas still remains unexplained, especially since the average duration of labor is reported to be the same for primiparas of all age groups.[26] The apparent similarities in the distribution of congenital craniotabes, or cranial osteoporosis, and intracranial birth trauma may be only coincidental; they are nevertheless provocative and deserve investigation.

The relationship of congenital cranial osteoporosis to intracranial birth hemorrhage could, perhaps, be better investigated by means of autopsy material. The incidence of congenital craniotabes among infants found to have died from intracranial birth hemorrhage should be compared with the average incidence for a given locality. In view of the characteristic seasonal incidence curve of congenital craniotabes,[1, 2, 12a, 14a, 15, 20b, 21] plotting a mortality rate curve for intracranial birth hemorrhage in relation to the month or season of birth for comparison with the seasonal incidence curve of congenital craniotabes in the same locality might also contribute valuable information. Similar seasonal studies of retinal hemorrhages in the newborn infant might also be valuable. Since congenital cranial osteoporosis may be open to prophylactic measures,[2, 3, 5, 12-21] the problems outlined are of practical obstetric and pediatric importance.

SUMMARY

Congenital craniotabes, or cranial osteoporosis, is studied in relation to certain etiologically important factors in intracranial birth trauma, such as cranial molding and duration of labor.

This study, supplementing an earlier investigation, now comprises 1,425 nonselected, apparently full-term newborn infants in Los Angeles and Mexico City, and the corresponding maternal obstetrical histories. It confirms the relationship of congenital craniotabes to cranial molding and separated cranial sutures as observed in the neonatal period, and rules out any re-

lationship to the type of delivery and duration of labor.

No published reports were found concerning the relationship of congenital craniotabes to any of these factors with the exception of separated cranial sutures.

This study provides the basis for a new approach to the problem of intracranial birth trauma, namely, investigating it in relation to cranial osteoporosis in the full-term infant, and thus supports a broader clinical concept of congenital craniotabes.

CONCLUSIONS

1. The soft, osteoporotic, and presumably more pliable, fetal skull presents no advantage obstetrically over the hard, normally calcified one, from the standpoint of either the average duration of labor in spontaneous births or the incidence of instrumental deliveries.

2. Cranial molding by overriding of sutures is more evident neonatally in infants with hard, well-calcified skulls, whereas widely separated sutures are more evident in infants with osteoporotic skulls, indicating that the molding mechanism may be influenced by the degree of calcification of fetal cranial bones.

3. The molding mechanism in either osteoporotic or osteosclerotic skulls may be etiologically related to intracranial birth trauma.

4. Since avitaminosis D during pregnancy may be responsible for the development of congenital cranial osteoporosis, the insurance of normal calcification of the infant's cranial bones by prenatal care, has practical obstetric as well as pediatric importance.

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THE DIAGNOSIS AND MANAGEMENT OF CONGENITAL HYPERTROPHIC PYLORIC STENOSIS

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A REVIEW of 100 consecutive cases of congenital hypertrophic pyloric stenosis has demonstrated that the diagnosis can be made by palpation of the tumor in 90 per cent of the patients. Severe dehydration, electrolyte disturbances, and malnutrition commonly encountered a decade ago are rare today. However, they do occur, and with the advances in fluid and electrolyte therapy such patients can be prepared more adequately for operation than in the past.

While the etiology of congenital hypertrophic pyloric stenosis is unknown, the pathologic changes in the stomach and pylorus have been carefully studied. The thickened, hypertrophied portion of the pylorus consists of the circular muscle layer, which on microscopic examination shows an actual increase in the number of cells as well as hypertrophy of the individual fibers. Initially, there is no histological evidence of inflammation, but later, edema and round-cell infiltration are present. It is this inflammatory process which may add the final element of obstruction and block the lumen completely.[1]

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This clinical report is based on 100 consecutive cases of pyloric stenosis treated during the six-year period from March, 1945, to October, 1951, and includes both ward and private patients. Some of these patients were treated on the private wards of hospitals other than the Boston Floating Hospital. The average age of our patients at the time of admission was 6 weeks. There were seventy-eight males and twenty-two females, giving a ratio of 3.6 males to each female. The average weight on admission was 8 pounds, and the duration of symptoms averaged slightly over two weeks. Vomiting and failure to gain, or actual loss in weight, were the chief causes for admission to the hospital. Projectile vomiting occurred in every patient. The vomitus was described as clear, not bile stained, and consisting of recently ingested formula in eighty-two cases. In four instances the vomitus was described as yellow, in three cases as containing blood streaks, and in one as coffee ground. In ten cases the character of the vomitus was not stated. After feeding, gastric waves were almost invariably present, but important diagnostic reliance cannot be placed upon this phenomenon since we have observed it in patients with intracranial hemorrhage and other unrelated conditions.

The diagnosis can be made accurately by palpation of the pyloric tumor, and this was accomplished in 90

per cent of our cases. In none of our patients did this finding prove wrong at operation. This examination should be performed with care and patience since the presence of a tumor clinches the diagnosis and makes further diagnostic procedures unnecessary. Palpation should be done while the child is eating or immediately after vomiting, when the abdominal wall is relaxed and the stomach is empty. With the examiner on the left side of the patient, the index and third finger of the left hand should be placed upon

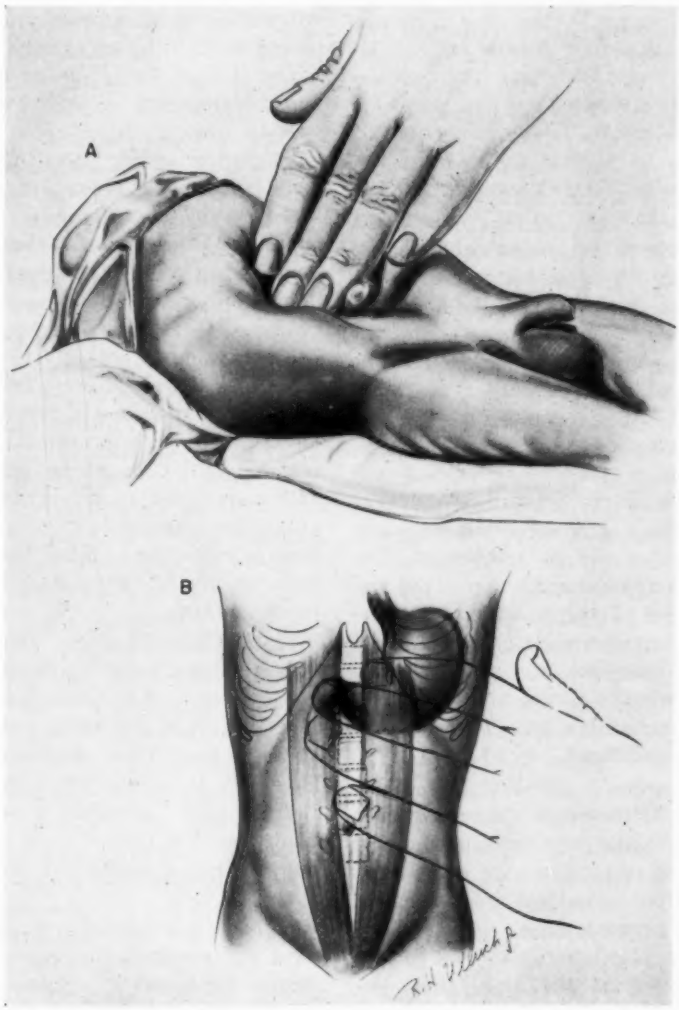

Fig. 1.—*A*, Method of palpation of the pyloric tumor. The examiner stands on the left side of the patient and uses the fingers of the left hand to palpate the mass. *B*, palpation is carried out through the right rectus muscle directly downward. Note how the tumor is engaged between the palpating finger and the spine.

the abdominal wall over the right rectus muscle above the umbilicus (Fig. 1, *A*). Palpation should be downward through the rectus muscle so as to compress the tumor between the examining fingers and the posterior abdominal wall (Fig. 1, *B*). The tumor mass must be rolled under the examining fingers to clinch the diagnosis. Frequently pyloric tumors are not detected because the examiner is on the right side of the patient and places his fingers lateral to the rectus muscle and attempts to palpate the pylorus upward against the soft structures to the right of the spine.

Patients without a palpable tumor, but with a typical history, are subjected to roentgen studies. Roentgenograms, with barium as a contrast medium, were done in nineteen of our cases, and in all instances the diagnosis of pyloric stenosis was made. This high incidence of x-ray examination is explained by the fact that some infants in whom we palpated tumors had been subjected to roentgen studies before admission. The typical x-ray showed a narrowing and elongation of the pyloric canal, and the diagnosis is made on this finding. Retention of large amounts of barium three and four hours after examination is suggestive but not diagnostic of this condition.[2, 3]

Twenty-five per cent of the patients in this series were diagnosed soon after the onset of vomiting when dehydration was minimal, and consequently no parenteral fluids were required preoperatively. In the remainder, blood was collected for determination of the bicarbonate, sodium, potassium, and chloride levels. A constant scalp intravenous was started and equal volumes of half normal saline and 5 per cent dextrose in water was administered. When the blood electrolyte values were reported, the fluid was changed to meet the known electrolyte requirements. In most instances the blood electrolyte values were normal and the same hypotonic fluid was continued. The volume given in a twenty-four-hour period is 50 to 60 c.c. per pound. In a few babies there was an alkalosis and in one patient the bicarbonate was 41 meq. per liter. This 7-pound baby had a serum potassium of 1.8 meq. per liter and demonstrated advanced electrocardiogram changes consisting of inversion of the T waves, lengthening of the Q-T interval, and depression of the S-T segment. In the course of three days 50 meq. per liter of potassium were given with a change of the blood level from 1.8 to 5 meq. per liter and a return of the electrocardiogram to normal. A good urinary output must be established and maintained to safely administer potassium intravenously. It has not been our practice to administer potassium unless the serum level has been below normal.

If the baby does not vomit after every feeding, small amounts of dextrose water may be given orally since some of this material will pass through the pylorus and be absorbed. However, if vomiting is severe or if the stomach remains greatly distended, gastric intubation is instituted and suction is continued until after operation.

It is now generally recognized by most pediatricians that early surgery is the treatment of choice for congenital hypertrophic pyloric stenosis. In the hands of experienced surgeons the operation immediately relieves the

pyloric obstruction, the mortality is low, and the babies are home from the hospital taking and retaining a full formula in a few days. The operation used today was introduced by Ramstedt and consists of splitting the hypertrophied musculature in a longitudinal manner. This permits the mucosa to pout outward, restoring the normal pyloric lumen.[5]

Ether is the anesthesia of choice and is administered by the open method with a stream of oxygen directed under the mask. This was the anesthetic agent in ninety-five of our cases, while cyclopropane was used in three instances, and a brandy nipple with local procaine infiltration was used in two.

The preferred incision is the gridiron, subcostal muscle-splitting type described by Robertson.[6] This incision was used in eighty cases, while in thirteen the incision employed was transverse, and in seven a right rectus muscle retracting incision was used. Recently, the right subcostal muscle-splitting incision has been routine because with it the possibility of evisceration is eliminated. Care must be taken to incise the skin lateral to the edge of the rectus muscle so that a true muscle splitting of the three muscular layers of abdominal wall is possible (Fig. 2, *A*).

The practice of blindly grasping the pyloric tumor with an instrument to effect its delivery out of the wound is time-consuming and dangerous. A better maneuver is to grasp the easily exposed stomach and by traction deliver the pyloric tumor (Fig. 2, *B*). The pylorus is supported outside the incision by the operator's left index finger against the duodenal end and by the assistant grasping the stomach adjacent to the tumor (Fig. 2, *C*). The avascular area on the anterosuperior surface of the pyloric tumor is selected, and a longitudinal incision is made throughout its length, severing the serosa only. Utilizing a blunt instrument such as a scalpel handle or blunt-nosed forceps, the hypertrophied muscle fibers are easily spread, exposing the mucosa. This layer is completely exposed over the length of the tumor and will pout out of the incision when this maneuver is correctly accomplished. Extreme care must be taken not to open the mucosa. The point where this accident most often occurs is at the distal end of the pylorus where the tumor projects into the duodenal lumen, producing a pocket where the mucosa partially overhangs the edge of the tumor and is practically adjacent to the serosal surface. Should the mucosa be opened immediate repair must be performed to avoid contamination of the peritoneal cavity. Closure of the perforation is accomplished with interrupted, fine, chromic sutures, and the area covered by omentum as a safety measure. This complication occurred in 10 per cent of the patients in this series. The experienced operator rarely commits this error and in all instances of perforation in this series the operation was performed by a member of the resident staff. No complication resulted in any of these cases.

Little bleeding is present if the incision into the musculature is made in the correct avascular area. The oozing will stop when the pylorus is returned to the peritoneal cavity and the venous congestion relieved. Therefore, it is unnecessary to do anything to stop the bleeding from the incised pylorus. The pylorus is replaced in

the abdominal cavity and the wound closed in layers, using interrupted, fine, silk sutures to peritoneum, muscles, and fascia. The skin is closed with a layer of interrupted, 5-0, plain, catgut sutures placed in the deeper layers of the dermis. A gauze dressing is not applied; instead, great care is taken to achieve complete hemostasis, and the wound is covered with a thin layer of collodion.

By utilizing this type of skin closure there is no cumbersome dressing to be soaked with urine or vomitus and thus

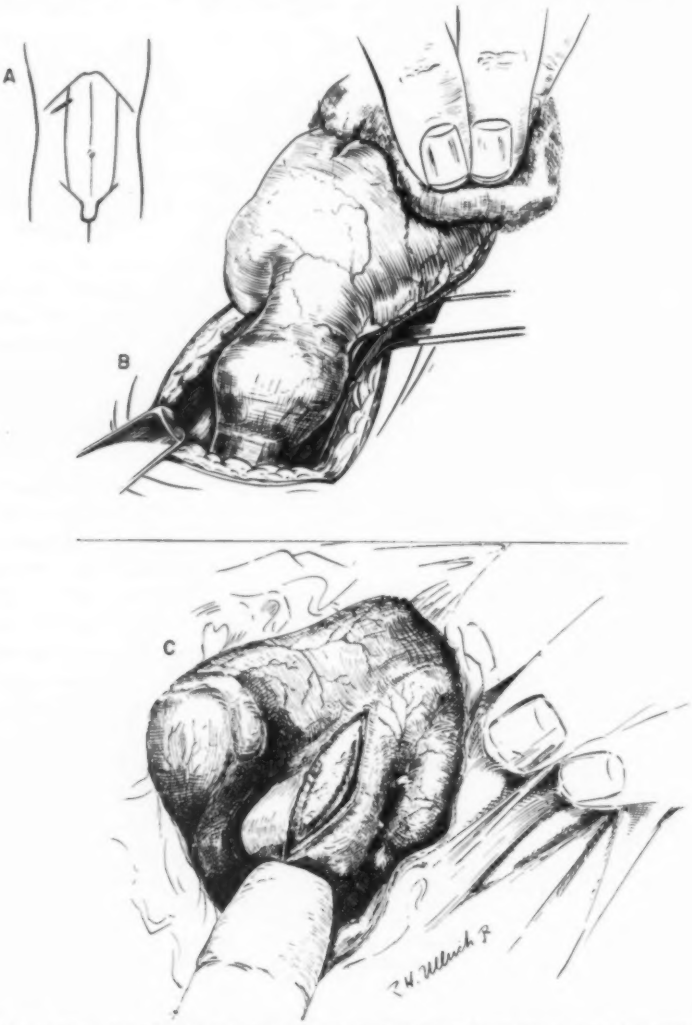

Fig. 2.—*A*, Position of right subcostal muscle-splitting incision lateral to the rectus border. The tumor is delivered into the wound by traction on the stomach. *B*, Assistant grasps the stomach to hold the pylorus in the field. *C*, Operator steadies the tumor with his left index finger. The hypertrophied muscle fibers have been split and the mucosa bulges along the entire length of the incision, restoring the pyloric canal.

serve to contaminate the wound. No changes of dressing are necessary, and since there are no sutures to remove, the infant may be sent home three to four days following the operation. The mother is advised that the collodion covering the wound will probably separate on about the seventh postoperative day.

Management of our cases has been simplified considerably by modifying the unnecessarily complicated postoperative feeding regimen which is usually recommended. As soon as peristalsis is audible, usually four to six hours postoperatively, the patient is started on 30 c.c. of 5 per cent dextrose in water solution every two hours. If this is tolerated for twelve hours the baby is given 30 c.c. of evaporated milk formula every two hours and the amount is increased so that by the end of forty-eight hours postoperatively a full formula is being given. It is not unusual for the patient to vomit once or twice postoperatively but unless the vomiting is repeated the formula regimen is not altered. On this plan of feeding 60 per cent of the babies had no postoperative vomiting, 35 per cent vomited only once, and in only 5 per cent did vomiting persist longer than two days postoperatively and require modifications in the feeding regimen.

Again, one should not overhydrate the postoperative patient with excessive amounts of parenteral fluids. On the above feeding plan a third of our patients required no postoperative fluids, the majority of these being patients in whom no preoperative deficits existed.

There were no major complications in this series. Several minor complications were recorded but none were of a serious nature. There were no deaths.

SUMMARY

The simplicity of the diagnosis is stressed. Palpation of the abdominal tumor can be accomplished in 90 per cent and is the most important diagnostic point.

Early diagnosis and prompt surgical therapy made parenteral therapy unnecessary in about 25 per cent of our patients.

Details of the operation are stressed, such as incision, treatment of the tumor, hemostasis, and wound closure.

A simplified postoperative feeding regimen is outlined.

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THE CONTROL OF RHEUMATIC FEVER RECURRENCES WITH SULFADIAZINE AND GANTRISIN

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INTRODUCTION

SINCE recurrences of rheumatic fever increase the liklihood of permanent heart damage, their prevention is considered most desirable. It has long been recognized that episodes of acute rheumatic fever, both initial and recurrent, are related to preceding upper respiratory infections, particularly those associated with hemolytic streptococci. This has led to the idea, confirmed later by numerous studies, that control of such upper respiratory infections by means of chemotherapy would reduce the incidence of rheumatic fever.

Since 1947 an organized program of sulfonamide prophylaxis for the prevention of recurrences has been carried out in selected cases from the Richmond Rheumatic Fever Clinic. This present report deals with the results of this form of therapy in 190 cases. It compares the recurrence rate with a group of untreated cases previously reported from this same clinic. It further compares the relative merits of Gantrisin* and sulfadiazine and points out the complications and problems encountered in this form of therapy. The question of sulfonamide versus penicillin as the drug of choice in this form of therapy is also discussed.

From the Departments of Pediatrics and Medicine, Medical College of Virginia, and the Richmond Clinic of Virginia State Rheumatic Fever Program.

*Supplied to this study by Hoffmann-La Roche, Nutley, N. J.

HISTORICAL

One of the most characteristic features of rheumatic fever is its tendency to recur. According to Hansen[1] there is the greatest likelihood of recurrences during the first year following an attack. He reports that two-thirds of the patients will have recurrences within a three-year period of time. Wilson[2] observed that the chances of recurrences are five times greater before the age of 16 than after that age. McCue and Galvin[3] found a recurrence rate of 61 per cent in a group of 225 cases followed in Virginia for a period of at least three years.

After the pioneer work in sulfanilamide prophylaxis by Thomas and France[4] and by Coburn and Moore,[5] various clinics began to use chemotherapy with a striking decline in recurrence rate. Dodge and associates[6] had a recurrence rate of only 2.2 per cent in a group of eighty-eight patients treated with sufanilamide as compared with a recurrence rate of 18.8 per cent in a control group of 101. Baldwin[7] found a recurrence rate of only 1.2 per cent in fifty-one patients on sulfadiazine for periods ranging from one to two years, whereas an untreated control group had a recurrence rate of 8 per cent. Hansen and co-workers[8] found a recurrence rate of 3.8 per cent in a treated group through 131 patient seasons, with a 53 per cent recurrence rate in the control group.

Rubbo and collaborators,[9] reporting on a series of 548 cases in England, found a recurrence rate of 3.2 per cent in a group treated with sulfanilamide, whereas they found a recurrence rate of 11.8 per cent in a group of untreated controls.

While the reports of these series were most encouraging, the finding of sulfa-resistant streptococci in Army and civilian studies gave impetus to prophylaxis with other drugs, particularly penicillin. Denny and associates[10] treated healthy Army trainees who showed evidence of streptococcal infections of the throat with penicillin. In 798 cases so treated, two cases of rheumatic fever developed, whereas seventeen cases of rheumatic fever occurred in the control group. Kahn and coworkers[11] in a Chicago school of 126 children with inactive rheumatic fever, treated some of the group with penicillin in dosages of 5,600,000 units for one week of each month with no recurrences. Others on lower dosages had an increase in recurrence rate. Massell and associates[12] in a series of thirty-four rheumatic children, found a recurrence rate of 6 per cent in the treated group and 50 per cent in the controls. Maliner,[13] in a small group of thirty-three cases, had no recurrences in those treated with penicillin troches for a short time, with a 6.6 per cent recurrence in the control series.

MATERIAL

In the past twelve years the Richmond Rheumatic Fever Clinic has seen approximately 2,000 patients referred by physicians because of suspected rheumatic fever or rheumatic heart disease. The complete study of these patients included a careful history, physical examination with special attention to the heart, complete blood counts, sickling preparation, urinalysis, stool examination, sedimentation rate, electrocardiogram, and chest x-ray or fluoroscopy. After thorough study almost 1,000 cases were considered to have or have had rheumatic fever at some time based on the criteria of Taran[14] and Jones.[15]

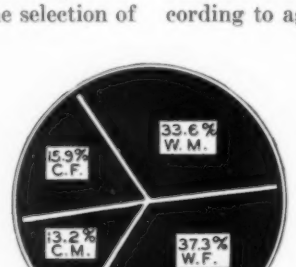
The present report deals with observations on 190 children with previous rheumatic fever who have been on continuous sulfonamide prophylaxis for periods varying from four days to seventy-six months. All patients have been followed from nine months to eleven years or an average of forty-four months in the Richmond Rheumatic Fever Clinic by the same group of clinicians at least two of whom participated in the evaluation of each case. Sixty-eight per cent of the cases were hospitalized in Richmond during the active stage in either acute or chronic wards and were under continued observation. The other 32 per cent were treated at home with periodic check-ups in the clinic. All patients who had received prophylactic sulfonamide under clinic supervision from August, 1944, to Oct. 1, 1951, were included. It was felt that those starting therapy after the latter date had not been maintained sufficiently long for an evaluation at the present time.

Selection of patients for sulfonamide prophylaxis was based on a number of factors. It was felt desirable to use prophylactic therapy in those cases which appeared more likely to have recurrences or in whom recurrences might be of more serious consequences. Such cases included those with recurrent attacks, those with residual heart damage, and those in the younger age group. It also included all those

who were hospitalized in convalescent wards since in most instances these represented the more severe cases. In addition to the above factors, the intelligence and cooperation of the parents had to be considered in the selection of cases. Every effort was made to educate the parents to the importance of regular dosage and laboratory studies. Thus, this is a highly selected group but weighed in favor of the more serious cases.

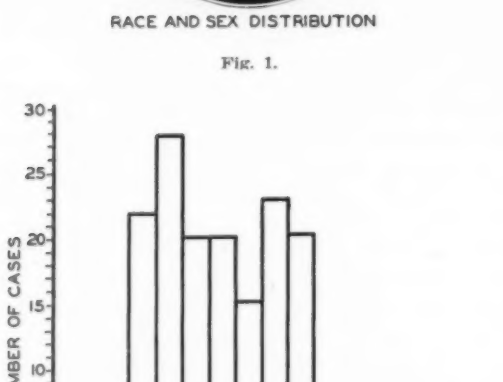
In the present series, there were 47 per cent males and 53 per cent females. The race distribution was 71 per cent white and 29 per cent Negro (Fig. 1).

The average age at the onset of rheumatic fever was 7 years. Fig. 2 illustrates the distribution of cases according to age.



RACE AND SEX DISTRIBUTION

Fig. 1.



DISTRIBUTION OF CASES ACCORDING TO AGE

Fig. 2.

Chorea was present in thirty cases (16 per cent). The cardiac status at the time prophylaxis was instituted is shown in Table I. Forty-three per cent showed no evidence of residual heart damage and were classified as potential rheumatic heart disease. Twelve of these had been considered to have

mitral "valvulitis" during the preceding acute episode because of the presence of definite "organic" murmurs, either systolic or diastolic. Since these murmurs may be the consequences of a transient and reducible active process involving the valve and may disappear (as it did in these cases) when the acute disease becomes quiescent, this term is felt to be preferable to the label of "insufficiency" or "stenosis."

TABLE I. CARDIAC DIAGNOSIS

Potential heart disease		82
(12 cases formerly mitral valvulitis)		
Rheumatic valvular disease		108
Mitral	83	
Aortic	6	
Aortic and mitral	19	
Cardiac enlargement		55

Fifty-seven per cent were classified as chronic rheumatic heart disease on the basis of "organic" murmurs persisting or developing after the active phase had subsided, indicating residual valve disease. As would be expected, involvement of the mitral valve predominated, occurring in eighty-three cases alone and in an additional nineteen with aortic valve disease also. The aortic valve was involved alone in only six cases. Fifty-five of these cases with residual damage demonstrated cardiac enlargement as determined by C/T ratio, either on x-ray or by fluoroscopy.

METHODS

The sulfonamides were administered in the following manner. The dose for children under 50 pounds was 0.25 Gm. twice daily. Those 50 to 100 pounds received 0.5 Gm. in the morning and 0.25 Gm. in the evening, while those over 100 pounds received 0.5 Gm. twice a day. The dosage was the same for Gantrisin or sulfadiazine. The few patients on sulfanilamide received 0.33 Gm. in two or three doses daily. The patients were directed to take their medicine at breakfast and supper.

Hemoglobin, leukocyte count, differential count, and urinalysis were done on each patient just prior to the institution of sulfonamide drug. The leukocyte count was repeated weekly for six times and a differential count also done if this showed a drop. For those hospitalized this study was completed before discharge. A urinalysis was repeated at the end of the first six weeks and subsequently as indicated. After the first six weeks white blood counts were ordered monthly for four times and then every three months for as long as the drug was used. Electrocardiograms, x-rays, sedimentation rates, and other tests were obtained periodically to determine the activity of the disease. Each referring physician received a letter outlining the plan and purpose of therapy, which emphasized the necessity of additional leukocyte counts in case of an intercurrent illness. Their cooperation in most instances has been excellent.

It was felt desirable to maintain a patient on sulfonamide prophylaxis throughout the year. Our previous study in Virginia indicated that, while recurrences were more frequent in the late winter and early spring, they did occur at any time throughout the year. In addition, frequent laboratory studies each fall were avoided by this continuous therapy. Unless complications arose, it was used for at least three years or until adolescence. Previous reports have clearly shown that the majority of complications will fall in this period.[1, 2]

The sulfonamides used in this study were sulfonilamide, sulfadiazine, and

TABLE II. DISTRIBUTION OF CASES ACCORDING TO DRUGS USED

Total Number of Cases		190
Sulfadiazine	124	(65%)
Gantrisin	53	(27.8%)
Gantrisin and sulfadiazine	11	(5.8%)
Sulfanilamide and sulfadiazine	2	(1.4%)

Gantrisin (Table II). Sulfanilamide was used in only two cases, and these were changed over to sufadiazine after a few months. Sulfadiazine was used from 1945 until 1950. Gantrisin was suggested then and has been used since for comparison, with the thought that it should have the advantage of any other sulfonamide in preventing streptococcal infections and, in addition, a low element of toxicity, especially as regards the kidneys. Eleven cases were changed from sulfadiazine to Gantrisin at the onset of this phase of investigation in the spring of 1950. The average duration on sulfadiazine was twenty-four months and on Gantrisin, eleven months. At this time sixty-three patients are still on sulfadiazine and forty-eight are on Gantrisin (Fig. 3).

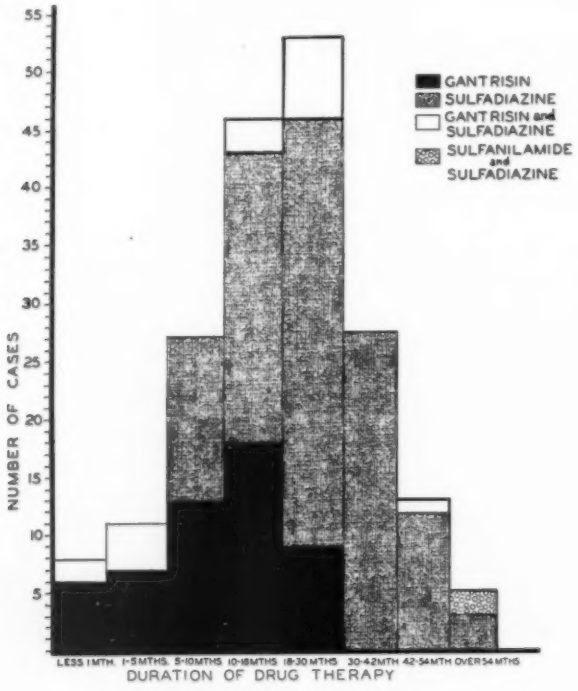


Fig. 3.

RESULTS

There were nine recurrences as shown in Table III. Two cases had recurrences of rheumatic fever with severe carditis on sulfanilamide the first year this therapy was being tried in Virginia. There were four recurrences in 135 cases on sulfadiazine

or 2.96 per cent. In three cases carditis recurred and in one chorea. They had been on the drug from five to thirty-six months. The recurrences on Gantrisin have been three cases out of sixty-four or 4.6 per cent. As will be noted, the first two of these patients had recurrences in less than two weeks after the drug was started. Since the latent period between the preceding infection and the onset of the manifestations of rheumatic fever may be as long as two weeks, we do not believe these should be counted as a failure of prophylaxis. Omitting these two cases, there was only one case in sixty-four giving a corrected recurrence rate of 1.5 per cent. This patient had severe carditis after seven months on Gantrisin. The recurrence rate for the entire series was 3.7 per cent excluding the two early Gantrisin cases.

The drugs were discontinued in seventy-eight cases for a variety of reasons as shown in Table IV. A leukopenia under 4,000 developed in 6.6 per cent on sulfadiazine, and 6.2 per cent on Gantrisin. In a few instances where the leukocyte count was between 4,000 and 4,500, the drugs were stopped because frequent rechecks were not possible. Others in this range, who could be observed closely, had no real trouble and the drug was continued.

The miscellaneous reasons for discontinuing sulfadiazine included one allergic rash, one rash and anemia, and one liver enlargement with positive thymol turbidity test. Three children on Gantrisin developed other illnesses. One child developed a severe diarrhea after one year on Gantrisin. This has since proved to be ulcerative colitis and a colectomy was done. One child developed an acute glomerulonephritis with a nephrotic syndrome. The third child had had recurrent hematuria from a urethral lesion prior to onset of rheumatic fever. After three months on Gantrisin, hematuria recurred. Since then, she has had intermittent urethral bleeding. With the exception of this case, which we believe is not related to the drug, no

TABLE III. RECURRENCES

		AGE	ATTACKS BEFORE SULFA	CARDIAC DIAGNOSIS	DURATION OF SULFA
Sulfanilamide	1.	6 WF	1	MI. MS. enlargement*	2 mo.
	2.	7 WM	2	AI.	16 mo.
Sulfadiazine	3.	5 WM	2	MI. MS. enlargement	18 mo.
	4.	8 WF	1	MI.	5 mo.
	5.	8 WF	2	Potential (chorea)	36 mo.
	6.	7 WF	1	MI. enlargement	14 mo.
Gantrisin	7.	16 WF	1	MI. MS. cardiac enlargement	2 wk.
	8.	17 WM	1	Pericarditis	4 da.
	9.	11 NM	2	MI. AI. enlargement	7 mo.

*MI. = Mitral insufficiency; MS. = mitral stenosis; AI. = aortic insufficiency.

TABLE IV. REASONS FOR DISCONTINUING DRUG

	SULFADIAZINE	GANTRISIN
Leukopenia		
Under 4,000	9 } 14	4 } 6
Under 4,500	5 }	2 }
Exacerbation	4	3
Local physician orders	6	2
Patient irresponsible	12	4
Miscellaneous	3	3
No longer needed	20	1
Total	59	19

hematuria was discovered on either sulfadiazine or Gantrisin. No known rashes occurred while patients were on Gantrisin.

DISCUSSION

The recurrence rate of 3.7 per cent in the present series when compared with a recurrence rate of 61 per cent in the group of 225 untreated cases previously reported from this clinic is quite impressive. It should be emphasized, however, that these two groups are not quite comparable and the untreated group cannot be considered a strict control. In the first place, as mentioned previously, the current series of treated cases is a selected group. In addition, there is a difference in time between the two groups, the original report covering a period from 1941 to 1946 and the second group of treated cases covering a period from 1947 to 1952. This difference in time has some significance because recurrences of rheumatic fever vary from year to year. Finally, the untreated group was followed for a longer period of time and had a greater chance to develop rheumatic recurrences. The present series has been followed on therapy for an average period of eleven months with Gantrisin and twenty-four months with sulfadiazine. Nevertheless, the two groups are comparable in race, sex, age, date of onset of rheumatic fever, and the percentage showing permanent cardiac damage. As such, the two groups had certain similarities which make the untreated cases a relative control. We, therefore, consider the marked reduction in recurrence rate as being significant.

There was no significant difference in the recurrence rate on sulfadiazine and Gantrisin. It should be mentioned, however, that the Gantrisin-treated group is smaller and was followed for a shorter period of time than the sulfadiazine-treated group.

The complications and hazards of such sulfonamide prophylaxis have to be carefully considered. While there are dangers of leukopenia, this complication occurred in only 6.8 per cent and under close laboratory supervision was promptly discovered and has not been a serious problem. In each case the white count has risen after withdrawal of the drug. The leukopenia under 4,000 on sulfadiazine being 6.6 per cent and on Gantrisin 6.2 per cent is not greatly different. The specific allergies were very few. The two serious illnesses developing on Gantrisin, namely, chronic nephritis and ulcerative colitis, are not believed by us to be related to the disease or therapy, although it is admitted freely that their exact nature is not understood.

One of the chief problems was educating the patients and their families in the importance of regular dosage and laboratory studies. The drugs were not continued when such cooperation was lacking.

While this study was concerned exclusively with the use of sulfonamides as prophylactic agents, it seems pertinent to say something regarding their comparison with penicillin. Having started with sulfonamides five years ago, we have continued this form of therapy in order to obtain an adequate series for evaluating its efficacy. We have had no personal experience with penicillin, but our results with sulfonamides compare favorably with those reported for penicillin, hence the two drugs appear to be equally effective. There are certain practical considerations, however, that makes it ap-

pear to us that sulfonamides are superior in some ways to penicillin. Penicillin has not been used long enough yet for a complete evaluation but it is noteworthy that there have been recent reports of penicillin-resistant streptococci[16, 17] which has been one of the objections raised as to sulfonamides. The fact that penicillin prophylaxis costs about $100.00 a year cannot be ignored by the average clinic group or family. Finally, penicillin has the disadvantage of being far more effective when given well before meals. This adds to the problem of this form of therapy in cases where children cannot be reached and given medicine at odd hours.

CONCLUSIONS

1. A brief historical review of sulfonamide prophylaxis in inactive rheumatic fever is presented with mention of recent comparisons with penicillin.

2. A group of 190 cases from the Richmond Rheumatic Fever Clinic was studied for recurrence rate and signs of toxicity on sulfanilamide, sulfadiazine, and Gantrisin prophylaxis.

3. Three and seven-tenths per cent of the total had a recurrence on a sulfonamide drug. During an average period of twenty-four months on sulfadiazine and eleven months on Gantrisin, there was a recurrence rate of 2.9 per cent on sulfadiazine and 1.5 per cent on Gantrisin. (The average period of each case followed was forty-four months.)

4. The complications of therapy were leukopenia in about 6 per cent on either drug. No related urinary symptoms were found. A few allergies and intercurrent illness are discussed.

5. The advantages and disadvantages of sulfadiazine and Gantrisin are about equal in the dosage used here.

6. The striking decrease in recurrence rate to 3.7 per cent contrasts sharply with a somewhat parallel group reported in 1948 from the same clinic with 61 per cent recurrences.

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BENIGN LYMPHOID HYPERPLASIA OF THE RECTUM

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LYMPHOMATOUS lesions of the rectum have been reported with increasing frequency in the last several years. That many of these lesions are apparently benign has been emphasized in several excellent reviews.[1-5] The problems of classification of the lymphomatous tumors on the basis of rigid histological criteria are apparent from the confusion in nomenclature. As a consequence it would seem desirable to replace a relatively static concept of these lesions with a more dynamic orientation. A concept entirely free of confusion must await clarification of the etiology of these lesions, however. Recent reviews by Custer and Bernhard,[6] Symmers,[7] Helwig and Hansen,[8] and Jackson and Parker[9] have done much to clarify the natural course and behavior of lymphomatous lesions. This clarification has been facilitated by the presentation in these reports of cases illustrating the coexistence of two lymphomas or the transition from one type to another.

The lability of these diseases renders the management and prognosis of any one patient a difficult problem. Simple lymphoid hyperplasia is intrinsically a benign lesion, but may also represent the earliest change seen in lymphoid tissue in which a more malignant lymphoma is developing. Lymphosarcoma and Hodgkin's sarcoma are extremely malignant. Giant follicular hyperplasia is intrinsically benign but extremely labile. The course of the lymphatic and monocytic leukemias and Hodgkin's paragranuloma and granuloma is rather variable.

These variations serve to emphasize that detailed case study and histological examination to determine the predominant cellular and clinical picture are a necessity for appropriate management of such cases. The following case reports emphasize several of the clinical problems these patients present to the physician. They also serve to illustrate that, although isolated lymphomatous lesions of the rectosigmoid have been reported most often in the adult, this diagnosis must be seriously considered in the differential diagnosis of rectosigmoid lesions in the pediatric patient.

CASE REPORTS

Benign Lymphoid Hyperplasia of the Rectum

D. L. (374-797), a 9-year-old white female, was admitted to the Research and Educational Hospitals of the University of Illinois on Dec. 12, 1950. Four weeks prior to admission a yellowish mucoid discharge from the rectum was noted. Examination elsewhere had revealed several polypoid lesions in the rectum just above the pectinate line. A biopsy was taken after proctoscopy; barium enema confirmed the findings and failed to reveal other pathology. The patient developed a fever of 104° F. immediately after the biopsy which subsided spontaneously. A diagnosis of lym-

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phosarcoma was made from the biopsy and the patient was referred to this hospital.

The patient had an appendectomy at age 2½ years. The maternal grandmother had an abdominal-perineal resection of the rectum for rectal cancer in 1949. Except for the continued mucous discharge the past history was otherwise noncontributory.

Physical examination revealed several discrete, nontender, freely movable, anterior cervical lymph nodes. There were several carious teeth. Rectal examination revealed three firm, wide-based, wartlike, nontender lesions just proximal to the pectinate line. These were not fixed to the perirectal tissue. There were no other abnormalities on physical examination.

Laboratory study revealed the following: Urinalysis was negative. Hemoglobin was 12.5 Gm. per cent. Hematocrit was 38 per cent. The blood count was 4.22 million and 6,850 leukocytes per cubic millimeter. Differential count showed neutrophils 50 per cent, monocytes 6 per cent, lymphocytes 39 per cent, eosinophils 4 per cent, and basophils 1 per cent. Nose and throat cultures showed no pathogens. National Institute of Health swabs failed to demonstrate the presence of *Oxyuris vermicularis* ova. There was no occult blood in the stool. Intradermal skin tests for tuberculosis and histoplasmosis were negative. Chest x-ray showed a nonspecific increase in the bronchovascular markings. Barium enema demonstrated a defect in the mucosal folds at the pectinate line. Proctoscopy to 20 cm. showed two polypoid lesions covered with normal mucosa at the pectinate line. These were about 5 mm. in diameter. Biopsies were taken from each.

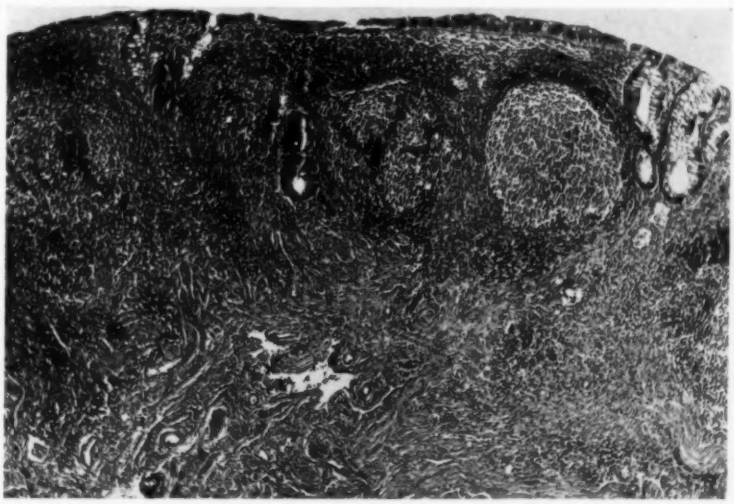

Fig. 1.

Examination of the biopsy specimens revealed compact polypoid structures with a moderately fibrosed submucosa surrounded with a mucosal layer, containing sparse glands in places due to displacement by lymphoid tissue in nodular form with large secondary centers. A representative section is shown in Fig. 1.

Attempts to excise the remaining portions of the still palpable polypoid lesions were unsuccessful as they were flattened out under the normal mucosa

when the proctoscope was introduced. Therefore, the patient was discharged, and when seen on Feb. 12, 1951, only one of these lesions was palpable. The patient developed measles after this visit. At subsequent examinations no lesions were palpable in the rectum. The child has been symptom-free except for a slight nonspecific mucoid vaginal discharge commonly seen in preadolescent females. There has been no change in the peripheral adenopathy.

The pathological picture of benign lymphoid hyperplasia and the absence of any evidence of systemic or local disease permitted a diagnosis of benign lymphoid hyperplasia of the rectum.

"Benign" Lymphoid Hyperplasia of the Rectosigmoid

R. B. (331-341), a white male, born July 29, 1936, was first admitted to the Research and Educational Hospitals on Aug. 12, 1947. In 1940 he had been examined and a moderate degree of nontender cervical adenopathy, hepatosplenomegaly, and an enlarged abdomen noted. A blood count and tuberculin skin test at that time were reportedly normal. The cervical adenopathy fluctuated rather markedly in size and in early 1941 he was found to have polypoid masses in the rectum. No other symptoms could be elicited and there apparently had been no fever throughout the course of the illness. A clinical diagnosis of Hodgkin's disease was made and roentgen therapy was given to the cervical glands. There was no appreciable change in the course except for the occurrence of multiple respiratory tract infections including three episodes of pneumonia until 1944 when he began to have intermittent episodes of crampy abdominal pain. This persisted to June, 1947, when an appendectomy was performed. At this time marked enlargement of the retroperitoneal lymph nodes causing partial obstruction of the sigmoid colon was noted. After the operation the child developed constipation and a mucoid rectal discharge.

The remainder of the history, the family history, and social history were noncontributory.

Physical examination on admission revealed a well-healed right rectus incisional scar, a mild seborrheic dermatitis, a smooth firm liver and spleen palpable 2 and 6 cm., respectively, below the right and left costal margins. There were small firm freely movable lymph nodes in the axillae, inguinal regions, and the anterior cervical chain. The lower abdomen was somewhat distended. There was a firm nodular mass in the left lower quadrant that seemed to be within the sigmoid colon. Rectal examination revealed multiple firm nodular lesions lining the rectum in a solid layer from 3 cm. proximal to the anus as far as the examining finger could reach. There was definite narrowing of the rectum. Proctoscopy was limited to 10 cm. by this narrowing but confirmed the findings noted on rectal examination with no normal mucosa visible due to the extensive "polyposis." It was the opinion of several examiners that these lesions were malignant.

Laboratory investigation revealed the following: The blood count showed 4.3 million erythrocytes and 11,000 leukocytes per cubic millimeter. The differential count showed 73 per cent neutrophils, 12 per cent monocytes, 13 per cent lymphocytes, 2 per cent eosinophils. Urinalysis was normal. The erythrocyte sedimentation rate (Wintrobe technique) was 26 mm. in one hour. Agglutination reactions for typhoid, paratyphoid A and B, proteus OX_{19}, and brucellosis were negative. The cephalin flocculation test was negative in forty-eight hours and the thymol turbidity was 20 units. The serum albumin was 4.5 and serum globulin 4.3 grams per cent. The blood nonprotein nitrogen was 24 mg. per cent. Examination of the bone marrow revealed no abnormality. Roentgenographic examination of the chest, long bones, and upper intestinal tract revealed no abnormalities.

Barium enema with air contrast demonstrated an extremely irritable colon most marked in the distal portions. present from the anus through the sigmoid. Due to poor emptying it was impossible to determine adequately if

Fig. 2.

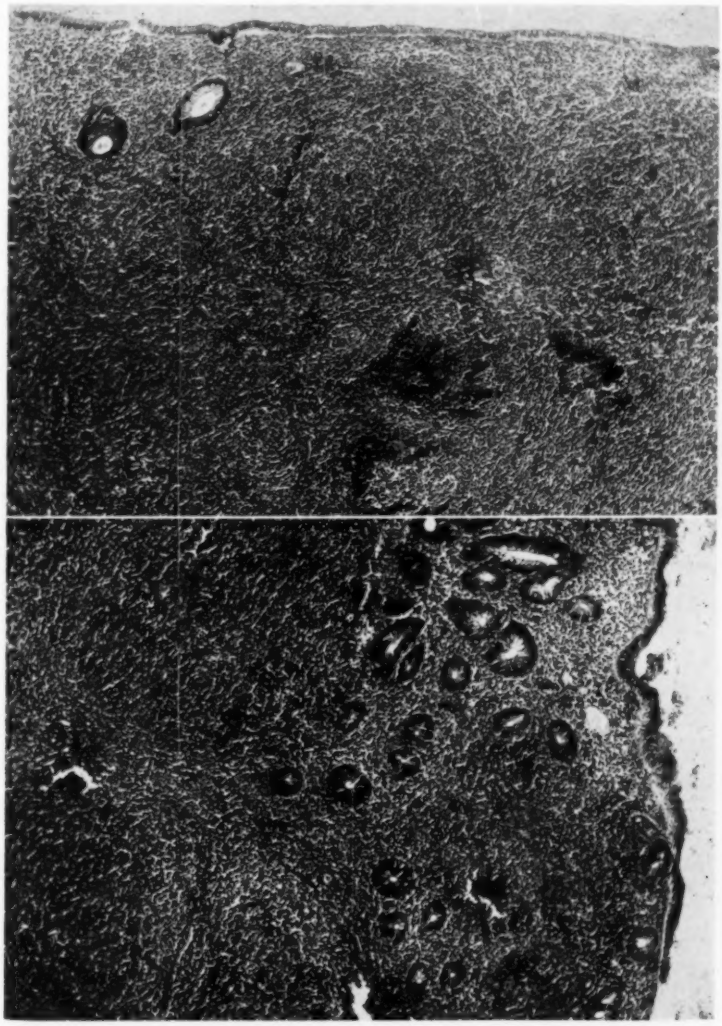

Fig. 3.

There was narrowing of the sigmoid and rectum. Mucosal defects suggestive of pseudopolyposis and dentate defects suggestive of ulceration were these findings extended as far as the splenic flexure. The enlarged liver and spleen were noted during these studies. Biopsies of the rectosigmoid

lesions were taken in August and November of 1947. One axillary node was biopsied in September, 1947, and a cell block was made of the rectal discharge.

The examination of the rectal discharge was not diagnostic revealing only many free polymorphonuclear and small round cells and a heavily infiltrated piece of mucosa. The biopsies from the rectosigmoid consisted of firm brown or tan tissue fragments about 1 cm. in diameter. Microscopic examination of the biopsies in August, 1947, showed tissue of polypoid form with massive infiltration of the mucosa and submucosa with lymphocytic cells associated with rather ill-defined secondary centers. As a result of the lymphoid hyperplasia both displacement and loss of glands as well as elongation and marked hyperplasia of the remaining glands were noted. A representative section is shown in Fig. 2.

The microscopic examination of the tissue from the biopsy in November, 1947, showed the same picture as that of August except that the changes were less marked. There was less distortion of the glands. The infiltration was less marked and more nodular with better defined secondary centers. A representative section is shown in Fig. 3.

The axillary node biopsied was rather firm. The cut surface was a homogenous pale tan. Microscopically, a moderate lymphoid hyperplasia with poorly defined cortical centers was noted. The sinuses were wide and very active with marked proliferation of the litoral cells and infiltration by numerous polymorphonuclear cells in some areas. The node is basically one of active lymph drainage with moderate lymphoid hyperplasia. A representative section is shown in Fig. 4.

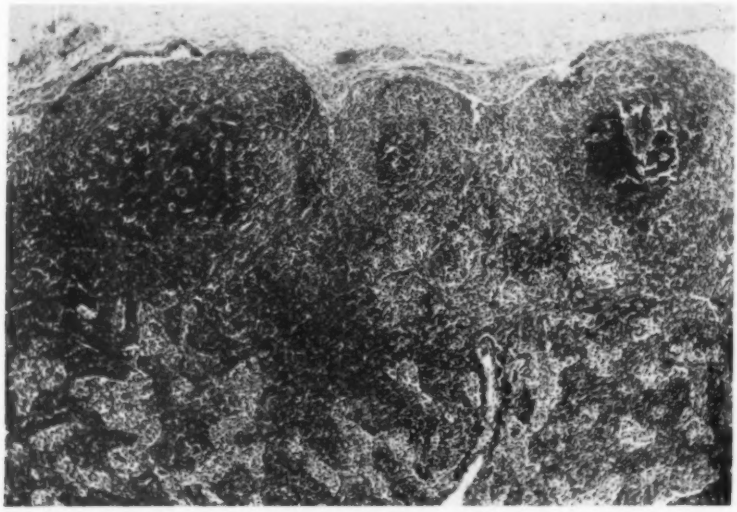

Fig. 4.

The degree of infiltration in the rectal lesions with the presence of large vesiculated nuclei in some cells was rather disturbing. Plasma cells and eosinophils which were present in some sections are not uncommon in lesions of the intestinal tract. In the absence of necrosis, fibrosis, and marked distortion of the normal architecture, it was felt that this pathological picture was one of extensive benign lymphoid hyperplasia. The lymph node presented a clear-cut picture of benign lymphoid hyperplasia.

The clinical picture, however, was in keeping with a more malignant process and a diagnosis of low-grade lymphosarcoma was considered although a definite diagnosis could not be made. In view of the minimal symptoms of partial intestinal obstruction and the evidence that this was probably a widespread process, surgical intervention was not considered indicated. From Jan. 15 to March 18, 1948, roentgen therapy totaling 450 roentgen units was administered to the pelvic areas. In February, 1948, the patient developed a serosanguineous rectal discharge that cleared by

Fig. 5.

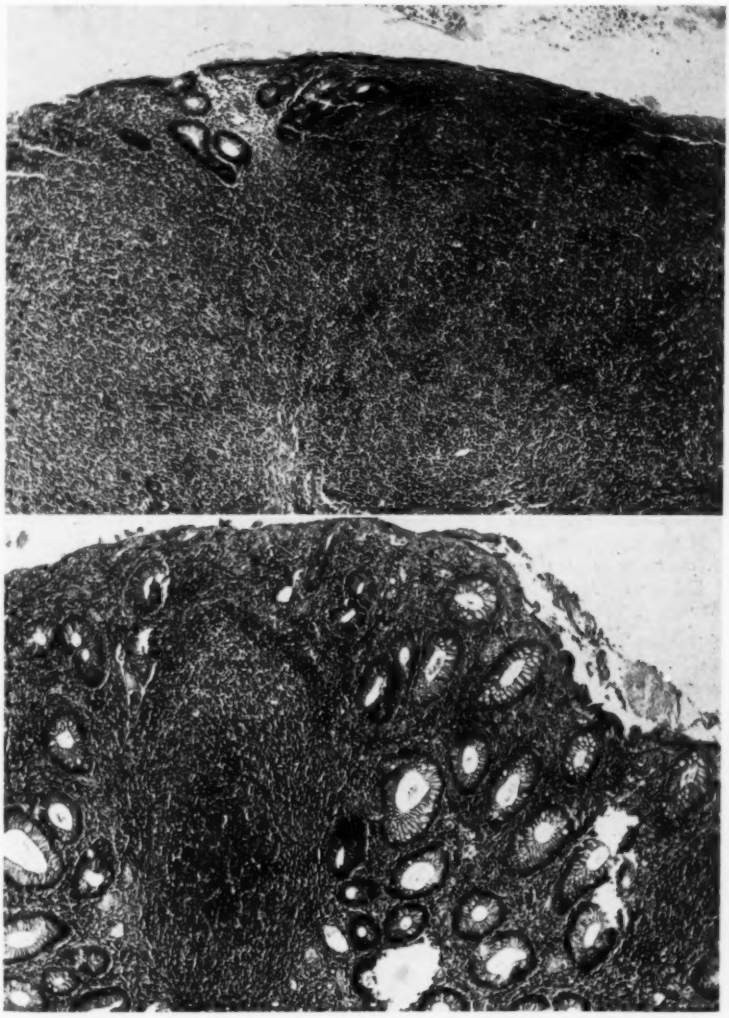

Fig. 6.

the completion of the roentgen therapy. There was a gradual improvement in the local findings with the stools becoming normal in size and consistency but with urgency and at times incontinence. The mass in the sigmoid area became smaller, more freely movable, and readily identified as the sigmoid colon. By September, 1948, the rectal lesions were smaller and could be identified as discrete nodular lesions instead of parts of a large mass. It was estimated that there had been about a 50 per cent improvement. There was no significant change in the peripheral adenopathy or hepatosplenomegaly.

The child was not seen again until July, 1951, at which time the findings were essentially as recorded above except that the entire descending and sigmoid colon was thickened, nodular, and less freely movable. During this interval he had been completely free of s y m p t o m s. Roentgenographic studies were essentially as described in the previous study, again inadequate for definite delineation of the extent of the lesions up the descending colon. Biopsy specimens were obtained from the rectosigmoid on July 12 and Oct. 24, 1951.

Five pieces of gray and tan tissue were obtained at biopsy in July, 1951. Microscopic examination of representative sections showed the same general picture as that seen in August and November of 1947 and described above. Microscopically, there was a more diffuse infiltration of lymphocytic cells and the secondary centers were less well defined than seen in the sections obtained in 1947. A representative section is shown in Fig. 5.

Only one "polyp" was obtained in October, 1951. This was a firm white piece of tissue with a stalk. Microscopically, there was little difference from the specimen obtained in November, 1947. Fig. 6 shows a representative section.

Both biopsies were considered to represent benign lymphoid hyperplasia pathologically.

The asymptomatic course has continued except for a minor rectal hemorrhage after the last biopsy which did not require therapy. Surgical intervention is still not considered warranted as there is no evidence of malignant degeneration. Future management will depend upon the symptomatology manifested by the patient and the findings on examination and by serial biopsies.

DISCUSSION

The term lymphoma includes all tumors made up of lymphoid tissue, malignant, benign, or leukemic. In any one patient the histological picture will not only vary at different times but at any one time may show lesions representative of several of the following more classical pictures and the less definite transition from one stage to the next. Fig. 7 is an attempt to diagram this dynamic concept.

Lymphoid hyperplasia consists essentially of an increase in the size and/or in the number of the lymph follicles. There is no destruction and only minimal distortion of the normal architecture. Mitotic figures and pleomorphism are present to variable degrees. These benign changes may persist in this form or undergo complete resolution or transition to a more malignant form of lymphoma. Lymphoid hyperplasia is the e a r l i e s t change seen in the development of the malignant lymphomas. When it is present in a submucosal area causing a mass, the resulting lesion has been termed variously a benign lymphoma, lymphadenoma, lymphadenoid polyp, or benign lymphoid polyp.

Giant follicular hyperplasia is differentiated from lymphoid hyperplasia by the much more extensive hyperplasia with marked variation in the

size and shape of the follicles. There is obliteration of many or all of the lymph cords and sinuses. The follicles are delineated by a zone of closely set, deeply staining lymphocytes which may be broken in places. Mitotic forms are common and the cell type varies from shadow cells to large lymphocytes. All changes are limited to the lymph follicles.

This form of lymphoma is intrinsically benign causing symptoms only by pressure on vital structures when the hyperplasia is marked or located in a critical position. The lymphoid tissue involved may be localized early but ultimately many different areas become involved including the spleen in most cases. The significance of this lesion lies in the frequency with which transition to a more malignant form of lymphoma has been noted. Custer and Bernhard[6] and Symmers[7] have reviewed this subject, noting the transition to any of the forms of Hodgkin's disease, lymphatic leukemia, and lymphosarcoma. Giant follicular hyperplasia can be relatively well controlled with roentgen therapy. In known cases which become resistant to such therapy the development of a more malignant lymphoma should be suspected.

The histological classification of Hodgkin's disease suggested by Jackson and Parker[9] and modified by Custer and Bernhard[6] is based on the predominant cellular pattern. The occurrence of different patterns in different areas of lymphoid tissue as well as in local areas at any one time may lead to a false classification if based on a single or inadequate biopsy. The clinical course of Hodgkin's disease is characterized by partial remissions with subsequent exacerbations terminating fatally after a period varying from months to many years.

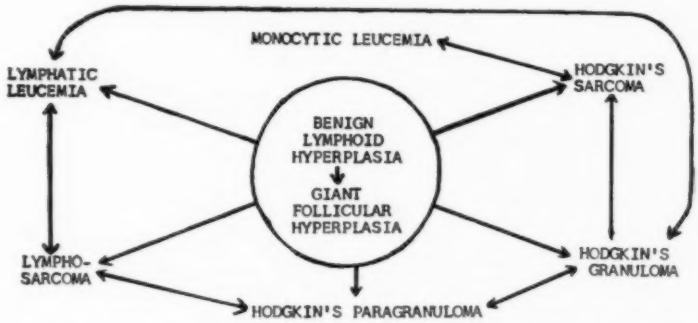

Fig. 7.—A diagrammatic representation of the dynamic relationship between the various lymphomas.

Hodgkin's paragranuloma is the most benign form of Hodgkin's disease. The lesions are more localized and the clinical course is longer with more minimal symptomatology than in other forms. The pattern of lymphoid hyperplasia is altered by the formation of sheets of lymphoid cells with partial to complete destruction of the normal follicle pattern. The predominant cell is the small lymphocyte with plasmocytes, reticulum cells, and Reed-Sternberg cells present but in relatively small numbers.

Hodgkin's granuloma is the classical form of the disease. The course is usually more abbreviated and the systemic symptoms more marked. Hepatosplenomegaly usually occurs earlier in those cases in which the abdominal lymph nodes are mainly involved in contrast to when mediastinal nodes predominate. The histological pattern is characterized by obliteration of the normal architecture and the appearance of more Reed-Sternberg cells, reticulum cells, plasmocytes, and eosinophils than are seen in paragranulomas. Extension to the capsule may occur. Varying degrees of necrosis and fibrosis are always present.

Hodgkin's sarcoma and so-called reticulum cell sarcoma are classified together as Hodgkin's sarcoma. Reed-Sternberg cells do not occur in the predominantly reticular cell forms. Both show considerable variation in the histological pattern from a well-differentiated reticulum cell pattern to a markedly anaplastic syncytial pattern. Lymphocytes, small or large, predominate. This is the most malignant form of Hodgkin's disease.

The transition of one form of Hodgkin's disease to another, the possible transition from all forms to lymphosarcoma, and the transition to lymphatic and monocytic leukemia have been well discussed in several reviews.[6, 7, 8, 9]

Lymphosarcoma generally runs a short course. There is complete destruction of the normal lymphoid follicle pattern by a dense infiltration of either predominantly small or large lymphocytes with infiltration of the surrounding tissues. There is no increase in the reticulum. Necrosis is commonly found. This process tends to extend by direct invasion but metastases do occur.

Lymphosarcoma often develops from giant follicular hyperplasia. The transition from lymphosarcoma to lymphatic leukemia occurs and vice versa. Lymphatic leukemia may also undergo transition to Hodgkin's disease.[10] The histological picture in the lymphoid tissue involved in lymphatic leukemia is the same as that seen with lymphosarcoma and the two must be differentiated by study of the peripheral blood and bone marrow. In the case of lymphatic leukemia the predominant cell seen in the lymphoid tissue is the same as that found in the bone marrow and the degree of cell differentiation depends upon the type of leukemia.

The importance of accurate interpretation of the histological picture in conjunction with intensive and continual evaluation of the total clinical picture is well illustrated in the case of D. L. cited above. The initial diagnosis of lymphosarcoma with the associated poor prognosis was very disturbing to the family. This interpretation is understandable, however, because, as pointed out by Heller and Lewis,[4] the histological picture of benign lymphoma of the rectum illustrated in Fig. 1 resembles malignant lesions of this area. There is destruction of the muscularis mucosa presumably due to pressure atrophy. As the lymphoid follicles of the gastrointestinal tract normally have no capsule, the interpretation is made more difficult. The lack of a capsule permits some diffusion of lymphocytes. Primary lymphoma of the rectum is rare but as part of a general malignant lymphoma is more common than benign lymphoma. The histological

diagnosis must be based on the presence of the essentially normal architecture of the hyperplastic follicles. In order to determine that the local lesion is not the early manifestation of a more malignant form of lymphoma, which may already be present elsewhere in the lymphatic tissue, a thorough evaluation of the patient is necessary initially and at repeated intervals. The work of Burke, Lavela, and Kaump[11] indicates that infection may be a factor in lymphoid hyperplasia and should be considered in the evaluation of the total picture.

The reviews by Helwig and Hansen[8] and Li[1] point out that the benign lymphoma of the rectum may be single or multiple. There may be no symptoms or there may be bleeding, mucous discharge, pain, diarrhea, or constipation. They emphasize that these are benign lesions which do not recur after excision, and may resolve spontaneously. While this is true in the majority of the cases there are relatively few cases which have been observed longer than five years. Recognizing the variable course which may characterize any lymphoma, these patients should be studied carefully for long periods to detect early and more malignant changes that may develop, and for the occurrence of new lesions. Wherever possible all rectal lesions diagnosed benign lymphoid hyperplasia should be removed surgically.

The disease, in the case of R. B. cited above, presents a less benign clinical picture. While the histological picture is interpreted as benign lymphoid hyperplasia the extensive involvement of the bowel with generalized lymphadenopathy and hepatosplenomegaly is more suggestive of Hodgkin's granuloma. The response to x-ray is compatible with this diagnosis also. Symmers[7] and Ewing[12] have both reviewed a condition first described by Briquet in 1838 and questionably termed "gastrointestinal pseudoleukemia." The picture presented by this condition is one of extensive lymphoid hyperplasia of the lymph follicles of the gastrointestinal tract with resultant polypoid lesions crowded so closely together that the normal mucosal pattern is completely obliterated. This extensive involvement may extend from the base of the tongue to the anus or involve only a portion of the gastrointestinal tract. There is associated lymphadenopathy and hepatosplenomegaly of varying degree due to the generalized lymphoid hyperplasia. The symptoms manifested by the patients may include melena, diarrhea, constipation, complete or partial obstruction at varying sites along the gastrointestinal tract, or a mucous discharge from the rectum. The lesions respond well to roentgen therapy.

Where does this condition fit into the classification of lymphoma? It can best be considered a transitional form from simple lymphoid hyperplasia to one of the more malignant patterns. In the cases reported to date this transition has not proceeded to the more malignant lymphomas during the periods of observation. Green, in the discussion of Sniderman's paper[3] on benign lymphoma of the rectum, mentioned a case in which there was a large area in the rectum of benign lymphoid hyperplasia which caused definite narrowing of the rectum. Several biopsies had confirmed the diagnosis. It became necessary to resect the lesions at which time the sections revealed lymphosarcoma at

the base of the lymphoid hyperplasia. Unfortunately no photographs of the sections were included but this may represent an example of a malignant lymphoma developing from extensive simple lymphoid hyperplasia instead of persisting as the picture described above in case R. B. The appearance of eosinophils, plasma cells, and many atypical and pleomorphic lymphocytes in the sections from case R. B. cited above is of little significance as these findings are common in lesions of the bowel wall.

The clinical picture in R. B. is most suggestive of Hodgkin's granuloma. The history of eleven years' duration of the findings with no progression and some resolution after roentgen therapy three years ago is less compatible with this diagnosis. The biopsies are not compatible with such a diagnosis. On the other hand, the picture of widespread involvement of lymphoid tissue is not compatible with the diagnosis of benign polypoid lymphoid hyperplasia of the rectum. This clinical picture is therefore considered a transitional stage between lymphoid hyperplasia and one of the more malignant lymphomas. The prognosis must be cautious therefore but the prolonged course without malignant transition may be considered encouraging.

It is apparent that surgical excision of the intestinal lesion in such cases as R. B., except in the treatment of complications, will be of no value as the disease is a disseminated one. The management of the case will perforce be limited to symptomatic treatment by roentgen therapy or chemotherapy. The exact therapy should be varied, depending upon the histological picture and the patient's response at any one time. Other supportive measures will be needed from time to time with the hazard of intestinal obstruction or hemorrhage being ever present.

The management of cases such as these is facilitated by a concept of lymphoma that includes in its framework the dynamic factor of transition from one form to another. At the same time the physician in accepting such a concept must also accept the responsibility of continual close observation of the patient in order to detect any transition. The prognosis given the patient at any one time may have to be changed. The life expectancy of a patient with one of the lymphomas can be greatly increased with proper treatment, both definitive and supportive.

Isolated lymphomas which are not extensive and show no evidence of generalized involvement of the lymphoid tissue may be excised surgically. The more malignant and more widely disseminated lymphomas are best treated with roentgen therapy or chemotherapy. Unfortunately the more malignant the lymphoma the poorer the response to therapy. The response to any therapy must be very critically assessed in view of the wide variations in the natural course of all these lesions. In the case of benign lymphoid hyperplasia true cures are to be expected. In other lymphomas, treatment must be considered palliative although in some cases cure is apparently effected. Palliative treatment in some instances will be compatible with a relatively good life expectancy.

SUMMARY

One case of benign lymphoid hyperplasia of the rectum is presented, with

the formation of several polypoid lesions and apparent spontaneous resolution. One case is presented showing by roentgen study complete obliteration of the normal mucosal pattern in the rectosigmoid associated with hepatosplenomegaly and generalized lymphadenopathy. This case is considered a transitional form between benign lymphoid hyperplasia and one of the more malignant lymphoma. Good results were obtained with palliative roentgen therapy. A serous discharge from the rectum should always suggest the possibility of a lymphoma of the rectosigmoid.

A dynamic concept of the lymphomatous diseases is outlined to facilitate understanding and management of individual cases.

The author is greatly indebted to Dr. Cecil A. Krakower, Professor of Pathology, University of Illinois College of Medicine, for the histological interpretation of the pathological specimens obtained by biopsy.

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APLASTIC ANEMIA FOLLOWING TWO DAYS OF CHLORAMPHENICOL THERAPY

Case Report of a Fatality in a 6-Year-Old Girl

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A RECENT editorial concerning blood dyscrasias[1] associated with chloramphenicol therapy prompted publication of this report. A fairly extensive search of the literature did not reveal any report of a fatality due to aplastic anemia after a short course of treatment with chloramphenicol. Previous reports have described the development of aplastic anemia after prolonged and intermittent use of this drug in the adult patient.[2, 3, 4, 5]

CASE REPORT

A 6-year-old Caucasian girl was admitted to the U.S. Naval Hospital, Philadelphia, Pa., Feb. 5, 1952, because of a petechial rash of the arms and legs associated with bleeding gums of about two weeks' duration. She was well until the middle of December, 1951, when she developed a febrile illness which was unrecognized for two days as the prodrome of rubeola. During these two days, prior to the appearance of the rash, she was given a 250 mg. capsule of chloramphenicol four times daily for two days. The total dose of this drug was 2 Gm. Prior to the first dose of chloramphenicol she was given a 250 mg. capsule of aureomycin which was vomited immediately. No other drugs were given during either the prodromal or exanthematous phase of her illness, with the exception of an occasional 0.3 Gm. tablet of acetylsalicylic acid (aspirin). The patient's father was a physician and was certain that she had not received chloramphenicol prior to this illness.

She had recovered completely from the measles by the second week of January, 1952. In the next few weeks she became progressively paler and listless. Her parents noted that she bruised easily and that she had frequent nosebleeds for the first time in her life. The gums bled so easily that brushing her teeth with a toothbrush was no longer possible.

The past and family histories were noncontributory. There was no history or family history of hay fever, urticaria, asthma, or blood dyscrasia. Her only previous illness was an attack of otitis media treated with penicillin three years before the present illness. Physical examination revealed a well-developed and well-nourished pale girl who weighed 62 pounds. She had an extensive petechial rash over the arms and legs. Scattered petechiae were seen in the roof of the mouth. The gums were boggy and over most of the teeth there were dried blood clots. Jaundice was not apparent. The spleen was not enlarged. Over the thighs and calves were many large ecchymotic areas. The Rumpel-Leede phenomenon was strongly positive. The erythrocyte count on admission was 1,750,000 with 5.5 Gm. hemoglobin. The leukocyte count was 5,400 with 10 per cent neutrophils and 89 per cent lymphocytes. There was 1 eosinophil. The platelet count was 100,000. Reticulocytes numbered 1.2 per cent. She had a prolonged bleeding time and poor clot retraction. Direct Coombs test was negative. Urinalysis was within normal limits. A

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The opinions or assertions contained in this article are the private ones of the writers and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

bone marrow smear three days after admission showed a striking absence of platelets. There were only 6 platelets in the whole slide. Megakaryocytes were absent except for one with poor nuclear morphology. The myeloid and erythroid elements were essentially normal. A second bone marrow slide five days later also revealed the marked paucity of megakaryocytes. The erythroid and myeloid elements appeared hyperplastic at this time. The peripheral blood counts continued to be pancytopenic. Representative peripheral blood counts during hospitalization are listed in Table I. During the entire period the patient received about two blood transfusions weekly as well as corticotropin (ACTH) 20 units twice a day for fourteen days followed by cortisone 10 mg. four times a day for the same length of time. As demonstrated in Table I this treatment had little effect on her blood count. A splenectomy was performed March 12, 1952, because of the possibility of hypersplenism. Little change was noted in the patient's health after this operation. Despite blood transfusions, twice a week, her blood counts manifested constantly a depression of all formed blood elements. Her course was inexorably downhill with frequent episodes of unexplained fever, treated with penicillin, melena, hematemesis, and showers of petechiae over the body. Bone marrow slides obtained two months after hospitalization showed marked marrow arrest of both myeloid and erythroid elements. The megakaryocytes were virtually absent. She received two more courses of corticotropin (ACTH) and cortisone therapy (20 units of corticotropin [ACTH] twice a day for fourteen days followed by 10 mg. of cortisone four times a day for a similar period). On May 12, 1952, she went into coma with fixed dilated pupils and marked nuchal rigidity. Her body was covered with many new petechiae and blood was noted oozing from her nostrils and gums. She died four hours later with signs of central nervous system hemorrhage.

TABLE I. SUMMARY OF HEMATOLOGICAL FINDINGS

DATE 1952	R.B.C.	HG GM.	W.B.C.	PLATELETS	GRANULOCYTES %	LYMPHOCYTES %	MONOCYTES	EOSINOPHILS
Feb. 5	1,750,000	5.5	5,400	100,000	10	89		1
Feb. 11	2,500,000	7.5	4,100	116,000	4	96		
Feb. 18	3,100,000	10.0	8,000	76,000	3	96	1	
Feb. 25	3,000,000	7.5	3,400	86,000	3	94	1	2
Mar. 5	1,500,000	6.0	2,400	110,000	17	83		
Mar. 13*	3,200,000	9.0	4,300	118,000	7	90	3	
Apr. 3	3,300,000	8.5	4,500	66,000	7	93		
Apr. 29	1,980,000	6.5	4,450	55,000	10	90		
May 6	1,700,000	6.0	2,100	50,000	3	97		

*First count after splenectomy. Patient received 1200 ml. of blood the week prior to operation.

Necropsy was limited to a sternal marrow biopsy. The histopathologic examination of the marrow smear showed a predominance of fat and only about 5 to 10 per cent cellularity. The cells present were all in the erythrocyte series and nonsegmented. There were no cells of the granulocytic series and no megakaryocytes.

COMMENT

The secondary or toxic form of purpura occasionally noted after measles was considered at the time of the patient's original hospitalization. The consistent depression of all the formed blood elements in the peripheral smears with the rapid inexorable downhill course made this diagnosis untenable. The diagnosis of aplastic anemia was consistent with the clinical and laboratory data. Drugs have been considered the most likely cause

of this form of anemia.[6] With the exception of the one capsule of aureomycin, which was vomited immediately, and a few acetylsalicylic acid (aspirin) tablets, the only drug the patient received prior to illness was chloramphenicol. Warnings of the possibility of bone marrow depression following chloramphenicol administration have appeared.[7] The presence of the nitrobenzene radical in this drug led Smadel[8] to warn of its potential danger as a hemopoietic toxin. In a recent report of fatal asplastic anemia in children[9] it was stated that those who died of this disease had on previous occasions received relatively small doses of chloramphenicol for minor illnesses. Another recent article continued to support the generally accepted belief that aplastic anemia has usually followed prolonged intermittent chloramphenicol therapy.[10] Our fatality differed from these observations in that the drug was given for only two days to a child who had never received chloramphenicol prior to her present illness.

SUMMARY

A fatal case of aplastic anemia following two days of chloramphenicol therapy in a 6-year-old girl who had never received this drug previously is reported.

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ACUTE GANGRENOUS APPENDICITIS IN A PREMATURE INFANT

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THE purpose of this paper is to present the rare occurrence of an acute gangrenous appendicitis, present in a premature infant of 1,590 grams. Associated with this lesion was what we considered a prepyloric stenosis, or pylorospasm.

CASE REPORT

Baby girl P. was born on Aug. 3, 1951, weighing 3 pounds 9 ounces (1,590 grams). Examination immediately after birth revealed an apparently healthy premature infant. The mother was a 28-year-old multipara, this being her second pregnancy. Her prenatal course was uneventful, although she did have mitral heart disease. The delivery was done under spinal anesthesia, no premedication, and an adequate episiotomy. At the time of birth there was no evidence of any infection in the mother, and her post-partum course was entirely devoid of any complications, either of an infectious or cardiac nature.

The infant was placed in an incubator. Routine premature care was given, including vitamin K, suction as necessary, gradual introduction of feedings (the Breck feeder being used), and good nursing care. For three days her progress was excellent, with no episodes of cyanosis, temperature elevation, vomiting, or diarrhea. Stools were noted on the third day, described as soft and yellow. On the fourth day some regurgitation was noted. By the fifth day this regurgitation had developed into vomiting following each attempted feeding. Gastric feeding (after lavage) and tincture of belladonna brought immediate relief. However, gastric distention appeared and did not subside. A flat plate of the abdomen revealed the stomach to be largely distended with gas. A normal amount of gas appeared to be distributed through the small and large bowel. The picture was interpreted as consistent with pylorospasm, or early hypertrophic pyloric stenosis.

During the next twelve hours vomiting recurred and it became necessary to use subcutaneous fluids to combat dehydration. Penicillin was started because of the probability of an aspiration pneumonia. However, as the infant's condition was becoming worse and attempts to relieve the abdominal distention were not very successful, surgery was decided upon. No temperature elevation had been noted up to this time.

Under local anesthesia, a 2 cm. incision was made in the right upper quadrant of the abdomen. The pylorus was in spasm but the typical olive-sized tumor of hypertrophic pyloric stenosis was not present. The pyloric musculature was incised, and immediate passage of the stomach contents into the duodenum was apparent. Because of the critical condition of the infant, further exploration was decided against and the abdomen was closed.

Postoperative management consisted of subcutaneous fluids, penicillin, oxygen, and constant attention in the incubator. After twelve hours the infant was retaining fluids and dilute feedings were started. However, his general condition remained poor, with intervals of cyanosis. An ecchymotic area appeared for 2 cm. around the perianal region which later appeared gangrenous. More abdominal distention, vomiting, and cyanotic episodes occurred. A rapid downhill course ensued that ended in death at the age of 9 days (twenty-four hours postoperatively).

From the Department of Pediatrics U. S. Naval Hospital, Key West, Fla.

An autopsy* was obtained. The pertinent findings were as follows: The body was that of a normally developed, somewhat poorly nourished, premature, white, female infant, weighing 1,400 grams and measuring 39 cm. in length. The 2.2 cm. vertical upper midline abdominal scar was noted, showing firm partial healing with no local inflammatory reaction. Surrounding the anus was a shallow, wide ulceration of the skin, 2 by 3 cm., with a somewhat dry black margin. On opening the abdominal cavity, no free fluid was found. Thin fibrous adhesions were present between the under surface of the abdominal surgical incision and the underlying transverse colon. The stomach was completely collapsed and empty with normal mucosa. The pylorus was not grossly hypertrophied. There was no gross evidence at the time of autopsy of the muscle-splitting, longitudinal surgical incision performed on the pyloric sphincter, but black silk suture tying omentum over pylorus was noted. (Microscopic section failed to show the typical musculature hypertrophy.) The small intestine showed minimal dilatation with bile-stained soft material. No constricting congenital bands or other obstructions were found. The appendix, 1.8 cm. in length, was of a fish-hook shape, and presented extensive, thin, fibrous, periappendiceal adhesions. Its distal half appeared soft, gray brown, and gangrenous, being sharply demarcated from the contrasting proximal half which was dark red and edematous. There was marked thickening of tissues about the appendiceal artery. There was no free pus about the appendix. The cecum, ascending and transverse colons were moderately dilated by soft fecal material, while the descending colon, sigmoid, and rectum were constricted and quite empty. No gross anomalies were demonstrated in the abdomen.

*Autopsy performed by Lieutenant Commander Charles Bratenahl, MC, United States Navy.

DISCUSSION

The rarity and high mortality of appendicitis in the neonatal period are well known. The truth of this statement has been demonstrated by many studies. Abt[7] in 1917, in a review of all cases of appendicitis in children, found seventy-two cases under the age of 2 years, and only twenty cases under the age of 3 months. Wilson,[2] after reviewing the literature, found only fifteen cases under the age of 4 weeks, including four designated as prenatal.

The high mortality in this age group is emphasized by Greene,[4] who, on a study of 194 cases under the age of 10 years, presented a mortality of 44 per cent in those under the age of 2 years. Such high mortality has been reported by many authors.[1-3, 6-8]

The incidence of appendicitis in premature (and prenatal) infants is extremely low, very few cases having been reported. Wilson[2] reported four neonatal cases; all the infants died. The author's personal experience consists of one prenatal case; the infant recovered after surgery at 4 weeks of age, after having been treated for *B. coli* septicemia. Engstrom[5] reports a case of appendicitis in an infant weighing 1,290 grams. This infant died on the twenty-fourth day of life without benefit of surgery.

This high mortality rate can be correlated with the high incidence of peritonitis. Packard and McLauthlin,[6] in an analysis of 329 cases of appendicitis in children, found a 51 per cent incidence of local peritonitis and a 62 per cent incidence of diffuse peritonitis in those patients under the age of 4 years. The high incidence of peritonitis has been attributed to several factors. These include lack of development of the omentum[1, 3, 6, 9] which leaves the peritoneal cavity somewhat unprotected, the relative large size of the appendix as compared to that of the intestinal tract, with a meager blood supply rendering it more vulnerable to gangrene, and the thin-walled, inelastic appendix due to a predominance of lymphoid tissue, leading to

easy rupture. However, the most important factor stressed is the difficulty and lateness of diagnoses.

Early symptoms such as refusal to eat, irritability, pyrexia, and constipation should be regarded suspiciously. It is usually the later symptoms of peritonitis, such as vomiting and abdominal distention, with which the diagnoses are made.

In the case reported, the question of pyloric stenosis was raised as the distention was almost entirely gastric. An obstruction was evident and surgical intervention was required. The surgical risk was great, and the relief of the apparent obstruction at the pylorus deterred any further exploration. Autopsy findings, however, revealed the major pathology. The etiology here is most likely prenatal but its exact nature is quite obscure.

CONCLUSION

1. A case report is presented of the unusual occurrence of an acute gangrenous appendicitis in a premature infant weighing 1,590 grams.

2. A review of some literature on this subject is presented, together with a discussion.

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Clinical Conference

CONFERENCE AT THE RAYMOND BLANK MEMORIAL HOSPITAL FOR CHILDREN, DES MOINES, IOWA

LEE FORREST HILL, M.D., CHIEF OF PEDIATRIC STAFF

DR. HILL.—Our first two patients this morning are older children whose stories have much in common, but whose diagnoses are quite dissimilar. Dr. Couchman, would you tell us about the first case?

Case 1. Acute Leukemia Simulating Rheumatic Fever

DR. PHILLIP COUCHMAN (Resident).—This patient is a 17-year-old farm boy who was admitted to this hospital on Sept. 5, 1951, with the chief complaints of fever and of joint pains which had their onset some two and one-half months ago. The referring physician thought he probably had rheumatic fever, but wished to have this verified. He had been quite well until the latter part of June, 1951, when he developed an upper respiratory tract infection after swimming in a local lake. He was treated with penicillin and recovered, and remained well until July 20 when he suddenly developed pain in the right anterior chest. He was hospitalized in his home town. An x-ray showed pneumonia, and his sedimentation rate was found to be elevated. Antibiotics had no effect upon this illness. Pain developed in both hips and knees and in the left shoulder, but there was no swelling or redness of the joints. The right chest pain subsided, only to be followed by a pleuritic type of pain in the left anterior chest.

After seven days of hospitalization, a probable diagnosis of rheumatic fever was made by the family physician, and 200 mg. orally of cortisone daily was begun. A dramatic subsidence in fever and symptoms promptly followed. The sedimentation rate became normal. He was discharged from the hospital on August 11 with instructions to continue the cortisone at home and to restrict his activity. Some two weeks later the drug was stopped for one twenty-four-hour period. His temperature rose to 101.8° F., and the joint pains returned. Cortisone was resumed, but this time his symptoms were not controlled and he was referred to this hospital for further evaluation. There is nothing in his past or family history of significance.

Physical examination was remarkable only in the paucity of positive signs. As you see, he is a well-nourished muscular youth. He does not appear ill, nor did he at the time of his entrance examination. His color was good. His temperature was 99.0° F.; pulse, 112; and blood pressure 130/86. There was painful and definite limitation of external rotation of the left hip and there was deep tenderness to palpation over the left scapula. All other joints moved freely and there was no swelling or redness of any of them. The heart was not enlarged nor was there enlargement of

any of the lymph nodes. The teeth were in good repair, and the nose and throat were negative. Neurological examination, including eye grounds, was negative.

A number of laboratory examinations were made during the patient's stay in the hospital. His initial red blood count was 4,430,000 and the hemoglobin was 13.9 grams. His white blood count was 10,000 with 62 per cent neutrophils, 5 per cent band cells, 29 per cent lymphocytes, and 4 per cent monocytes. Repeated white blood counts and differential smears were made. On September 19, two weeks after admission, his white blood count was 3,150 and two days later it was 2,300. At this time the differential count showed 27 per cent neutrophils, 15 per cent band cells, 56 per cent lymphocytes, and 2 per cent monocytes. Examination of the stained smears by the hospital hematologist showed adequate platelets—by count, 208,708—and no immature cells. His red blood count was 4,290,000 and the hemoglobin was 11.7 grams. The sedimentation rate (Westergren method) varied from 51 to 88 mm. per hour. Repeated blood cultures were negative. Agglutination studies with typhoid O and H, paratyphoid A and B, proteus OX_{19}, and brucellosis antigens were all negative. Cold agglutinins were absent. The heterophil antibody titer was normal. Urinalysis on several occasions showed no abnormality. The Mantoux tuberculin test was negative. Spinal fluid examination was normal. Total serum protein was 6.9 grams, with albumin 4.2 grams and globulin 2.7 grams, albumin-globulin ratio 1.6. Alkaline phosphatase was 1.7 Bodansky units. Repeated electrocardiograms were also normal. X-ray films of the chest, hips, skull, and sinuses were negative. No abnormality of the heart silhouette could be made out on fluoroscopic or roentgenographic study.

The temperature showed daily elevations to 100° F. the first four days of his hospitalization, then a gradual increase in the daily spikes appeared and by the thirteenth hospital day, his temperature was 104° F. He developed localized tenderness over the right anterior iliac spine, over the crest of the left ilium, and above the right eye on his skull. The skin in these regions appeared normal except for slight localized edema in the tender area above the eye. The areas remained tender for three to five days and then improved spontaneously. Aside from his fever and these tender areas, his condition remained unchanged throughout his hospital stay.

He was given a four-day course of salicylate therapy with no apparent effect upon his temperature or on the pain.

Dr. Hill.—The patient's age of 17 years places him in that narrow zone of "no man's land" between pediatric and adult medicine. To bring in an "adult" point of view, Dr. Glomset has kindly consented to come over from the internal medicine service to discuss the differential diagnosis. I should tell you that he has been given no advance information about the case. Dr. Glomset.

Dr. Daniel A. Glomset (Internist).—My discussion today will differ from the usual case analysis in that I have had no time to organize my thoughts. I will describe, therefore, my mental peregrinations as I sat here listening to the case presentation.

This case illustrates a situation discussed before the American College of Physicians in 1949, namely, fever of undetermined origin. The conclusions of that session were that if one could not make a diagnosis with ordinary tests in two or three days, it was best to allow four to six weeks to elapse. Then, the diagnosis would usually be easy to establish. A lot of tests have been performed on this patient. Most of them have been within normal limits. This costs the patient a lot of money. Perhaps the best test is the test of time.

This patient presents a problem of prolonged fever unresponsive to antibiotics. Such a situation narrows our field of consideration.

One might think first of brucellosis. I understand he works on a farm. Brucellosis is often responsive to aureomycin and is usually associated with a positive serum agglutination. Two blood cultures were reported negative at the end of ten days and the laboratory here is acutely aware of the brucellosis problem. It is true that sternal marrow cultures may be positive when agglutinations and blood cultures are negative; nevertheless, we can almost eliminate brucellosis from consideration.

Tuberculosis might also be unresponsive to the usual antibiotics. If tuberculosis were the disease in question, it would probably be of the bovine type because of the negative chest x-ray. The bovine type is rare in Iowa, so I certainly feel that his illness is not tuberculosis.

Another class of febrile illness unresponsive to the antibiotics is the neoplastic. It is entirely possible that Hodgkin's disease, leukemia, or cancer could be responsible for this illness. Cancer rarely produces such a clinical picture in this age group. I have a patient with leukemia with an elevated white count and no lymphadenopathy or hepatosplenomegaly, hence the absence of these physical findings may not eliminate leukemia. The patient may have leukemia, lymphosarcoma, or Hodgkin's disease.

Rheumatic fever may also be unresponsive to the usual antibiotics. You may also have thought of this possibility because you have taken so many electrocardiograms. He could have had rheumatic pneumonia at the onset of his illness. This is the right age for rheumatic fever. Migratory pains are present in rheumatic fever. Lack of response to salicylates speaks against rheumatic fever, but the drug may not have been administered for a long enough trial period. He probably does not have rheumatic fever, but we cannot eliminate it completely. I do not believe serum agglutinations would be of diagnostic value.

A few more febrile illnesses unresponsive to antibiotics come to mind. The collagen diseases—particularly acute disseminated lupus erythematosus may present such a picture. The course here seems too long for the usual acute disseminated lupus erythematosus. I do not anticipate finding this condition. Nor would I consider trichinosis. There is no history of associates similarly affected, and no eosinophilia. There is little likelihood of Still's disease as the joints show no particular damage.

One striking feature in his case history is relief by cortisone. Of course cortisone relieves "everything." It relieves Hodgkin's, rheumatic fever, leukemia, lupus erythematosus, and brucellosis.

In summary, this boy has had fever, pneumonia, pain in the chest, both hips, knees, and shoulders, and recurrent, subcutaneous nodules. X-rays, blood tests, electrocardiograms have been of little help in the diagnosis. If I were caring for him, I would assume that he had rheumatic fever and would keep Hodgkin's disease, or some type of malignancy, in mind. I would treat him with heavy doses of salicylates for ten days, and if the fever was not relieved, would give cortisone a prolonged trial.

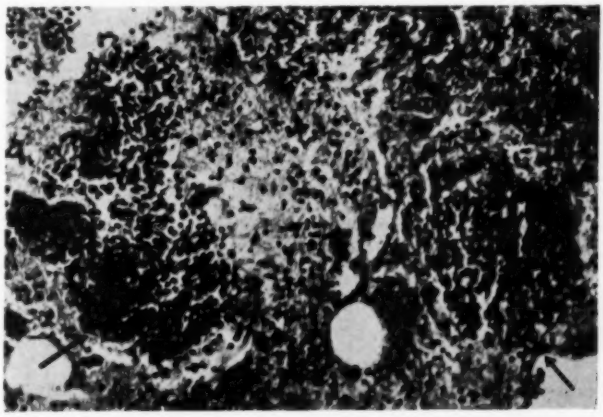

Fig. 1 (Case 1).—Bone marrow tissue. Peripheral blood smears normal. Note two islands of marrow tissue containing no fat. No megakaryocytes are present. The marrow is completely overrun with immature cells, mostly lymphoblasts.

Dr. Hill.—Thank you Dr. Glomset. Your remarks about the expensive work-up we have done on this patient are certainly apropos. In defense, I can only say that we were searching for some lead that would put us on the right track. Perhaps we should have done first what we did only two days ago. We did a bone marrow aspiration which showed a preponderance of large cells with large nuclei and scanty cytoplasm resembling immature lymphocytes. The hematological diagnosis is highly suspicious acute lymphocytic leukemia.

We have presented this patient today because his case illustrates so well several facts about leukemia. The first is the ease with which it may be confused with rheumatic fever. Second, splenomegaly, lymphadenopathy, anemia, and thrombocytopenia may all be absent early in the disease, but characteristic changes be present in the bone marrow. Likewise, blast forms may be absent in the peripheral blood, but present in the bone marrow.

Dr. Fife, will you tell us about the next case?

Case 2. Disseminated Lupus Erythematosus Simulating Rheumatic Fever

Dr. Reed Fife (Resident).—This patient is a 16-year-old white female who entered Raymond Blank Memorial Hospital with the complaints of nausea, fatigue, anorexia, migratory muscle pains, an eight-pound weight loss, and a history of intermittent low-

grade fever for two and one-half months preceding admission. The onset of her symptoms immediately followed a severe sunburn. Two weeks before admission, the family physician was consulted because of soreness in the left leg, hip, and neck. At this time he noted albuminuria and hematuria. The urinary findings did not clear following penicillin therapy. As the diagnosis of rheumatic fever was entertained, the patient was referred to this hospital for further study. Past history revealed repeated bouts of middle ear infection and mastoiditis. There was no history of exposure to tuberculosis. There had been no chills or dysuria. Neither raw milk nor well water had been ingested.

The physical examination on admission showed an alert girl, with good color, and in no distress. The blood pressure was 110/80. The temperature was 101° F. The pulse was 80 and it was regular. There was a residual pink scarring of the forehead and arm from exposure to sun. An area of atrophic skin was noted over the jugular notch. Gingivitis was marked. There was evidence of chronic bilateral otitis media. A funduscopic examination was negative. There were several enlarged cervical lymph nodes. The heart and lungs were normal. The liver edge was barely palpable. There was no evidence of edema or of joint or muscle tenderness or swelling. Neurological examination was within normal limits.

Laboratory studies were as follows: red blood count 4,500,000; hemoglobin 14.2 grams; white blood count 3,700 with 50 per cent neutrophils, 47 per cent lymphocytes, and 3 per cent monocytes. Repeated white blood counts over a three-week period showed a persistent leukopenia with count never exceeding 5,000. On one occasion the differential showed 10 per cent band cells. Sedimentation rate was 88 mm. per hour. A smear of the peripheral blood was normal. Adequate platelets were observed. Catheterized urine showed a specific gravity of 1.010; albumin, 1 gram; white blood cells, 2 plus; red blood cells, 1 plus. Hyaline and granular casts were present. Repeated urinalyses showed persistent microscopic hematuria, albuminuria, and cylindruria, and the specific gravity of random specimens was never above 1.017. Blood urea nitrogen was 19 mg. per cent; total serum protein, 5 grams with albumin 2.8 grams and globulin 2.2 grams; albumin-globulin ratio, 1.2. Serology was negative. Retrograde pyelograms were normal. Ureteral urine specimens were negative on culture. Bladder urine obtained at the time of pyelography yielded *E. coli* on culture. The intradermal tuberculin test was negative. Agglutination studies were not done. Bone marrow aspirations were studied and will be discussed subsequently.

The patient's course in the hospital was marked by an undulating type of fever with a maximum elevation to 103° F. Shortly after she was hospitalized, pain, redness, and swelling of the interphalangeal joints of the fingers occurred. On the thirteenth hospital day (after a diagnosis was made), cortisone therapy (15 mg. every six hours) was begun. A remarkable remission of symptoms occurred.

DR. HILL.—Dr. Byrum has prepared a differential discussion of this patient.

DR. R. J. BYRUM (Resident).—In the differential diagnosis of a prolonged febrile course such as this one, tuberculosis must be considered. Against this, is the negative skin test, no known contact with tuberculosis, a negative family history of the disease, and the use of pasteurized milk from tuberculin-tested cows. Syphilis can be ruled out on the basis of a negative serological test. Typhoid fever is a possibility; however, her course has been too long and she lacks the apathy which accompanies this disease. Splenomegaly and gastrointestinal symptoms are also lacking. It is, however, possible to have typhoid fever without these manifestations. The blood and urine cultures were negative for the typhoid organism. One should be suspicious of brucellosis. Again, the course in our patient is too long for an initial febrile reaction of brucellosis. The febrile episodes may last for one to two weeks, followed by periods of remission. The sedimentation rate is usually normal in this condition. Our patient's blood cultures were negative. However, the brucella organisms are difficult to recover. Infectious mononucleosis should be thought of. Against this is the leukopenia which has been present throughout. Although leukopenia is frequent early in the disease, a leukocytosis is eventually present. The prolonged febrile course is also against infectious mononucleosis. The blood smears were negative for the Downey cells. The spleen was not palpable; and, in about 50 per cent of the cases, this organ can be palpated. Unfortunately, a heterophil antibody titer was not done. Sarcoidosis might be considered. Fever is not usually seen in this condition; and, despite widespread involvement in sarcoidosis, the symptoms are more minor and less significant than those which we have here. Hyperglobulinemia, eosinophilia, and often adenopathy, along with cutaneous and osseous lesions, are a part of the picture. Acute glomerulonephritis is a possibility with the findings of albuminuria, hematuria, casts, and a somewhat low specific gravity. However, her course is not that of an acute hemorrhagic nephritis. There is usually oliguria, nitrogen retention, edema, and some degree of hypertension present. Leukemia is a possibility. In favor of this is the leukopenia and the presence of band cells in the smear of peripheral blood. Bone marrow examination would probably settle this problem.

Another group of diseases to be considered is the collagen or rheumatoid group. Scleroderma can be excluded as there are no typical skin changes, which, by this time, should be present. Dermatomyositis also has diagnostic skin changes. However, hematuria, albuminuria, and arthralgia usually do not occur. The white blood count is normal to elevated in that disease. Periarteritis nodosa would probably be associated with a secondary anemia by this time. Leukocytosis, eosinophilia, ecchymosis, and, oftentimes, nodules along the course of the blood vessels, are found in this condition.

One could make a diagnosis of rheumatic fever in this patient using Jones' criteria, as the girl has one major finding in migratory polyarthritis and two minor findings—the elevated sedimentation rate and fever. Leukopenia, albuminuria, hematuria, and the lack of cardiac involvement, however, are against this diagnosis. Rheumatoid arthritis should be mentioned. Against

this are the urinary and white blood count findings.

The disease that best fits the history and physical findings in this 16-year-old girl is the acute systemic form of disseminated lupus erythematosus. Symptoms first appeared after a severe sunburn. Cutaneous lesions may be absent in this form of the disease as they are in this patient. Prolonged fever, pains in the muscles and joints, leukopenia, proteinuria, and hematuria are characteristic of the disease. It shows a predilection for young females. In twenty-two of twenty-three cases reported, twenty-two were in females, and eighteen of these occurred in the second and third decades of life. The youngest was 7 years of age. Pericarditis, endocarditis, pleuritis, glomerulonephritis, perisplenitis, perihepatitis, degenerative changes in the skin, necrosis of lymph nodes, anemia, and leukopenia may all be part of the picture in this disease. Fibrinoid degeneration of the collagen and ground substance is the basic pathologic lesion.

We strongly suspected lupus before a bone marrow study was done a few days ago; and we were not surprised to have our suspicions confirmed by the demonstration of characteristic "L. E." cells in a bone marrow preparation (Fig. 2).

DR. HILL.—A good many years ago in my medical school days, Dr. John Morse emphasized the importance of examining the urine and the ears in children with unexplained fever. Later, blood cultures and spinal fluid examination, especially in young infants, were added. Now it would seem that the bone marrow should also be included as a profitable place to look in children with prolonged unexplained fevers. Dr. Birge, would you tell us a little about what can be learned from examination of the bone marrow?

DR. R. F. BIRGE (Pathologist).—Perhaps I can best illustrate the value of sternal puncture in febrile illnesses by citing a few recent experiences.

In the case under consideration, the diagnosis of lupus erythematosus was foremost in Dr. Kelly's mind. He, therefore, asked me to look for evidence of this disease.

When we examined marrow smears made at the bedside, we saw neutrophilic left shift, and that is about all. However, we also placed about 1 c.c. of aspirated bone marrow and blood in a Wintrobe hematocrit tube. After centrifugation we obtained the so-called buffy coat of hematopoietic cells. Smears prepared from the buffy coat about forty-five minutes after sternal puncture showed a peculiar change. We found so-called "L. E." cells as described by Hargraves.[1] One observes sticky clumps of neutrophilic leukocytes. One finds that some of these leukocytes have phagocytosed large rounded bluish masses of poorly stained nuclear material. Such degenerating nuclei are seen in various stages of digestion.

As you mentioned, we have studied recently the marrow of a boy who had unexplained fever. This boy's peripheral blood failed to show the presence of blasts or stem cells that we could expect to find in acute leukemia. However, the marrow picture was strikingly abnormal. Mounted microscopic sections of his marrow showed marked cellularity such as one sees in leukemia. Smears showed the presence of

large numbers of lymphoblasts and a paucity of normal erythropoietic and granulopoietic forms.

Not long ago a Negro boy, aged about 16 years, was admitted to the hospital with a febrile illness of several weeks' duration. We found granulomatous lesions in his marrow, and strongly suspect that they are tuberculous. A younger boy was seen in this hospital a few months ago; in his marrow we found tiny granulomas that constituted a histologic manifestation of brucellosis.

Granulomatous lesions occur in the bone marrow in tuberculosis, brucellosis, histoplasmosis, sarcoidosis, and perhaps other entities. There is not time to enlarge upon the value of marrow examination in other conditions such as the anemias. Suffice it to say that one should exercise his best judgment in selecting laboratory aids in diagnosis, and that this dictum applies to sternal puncture. Some fail to appreciate the fact that sternal puncture is occasionally a most useful procedure. On the other hand, a few have ordered the procedure indiscriminately with little benefit.

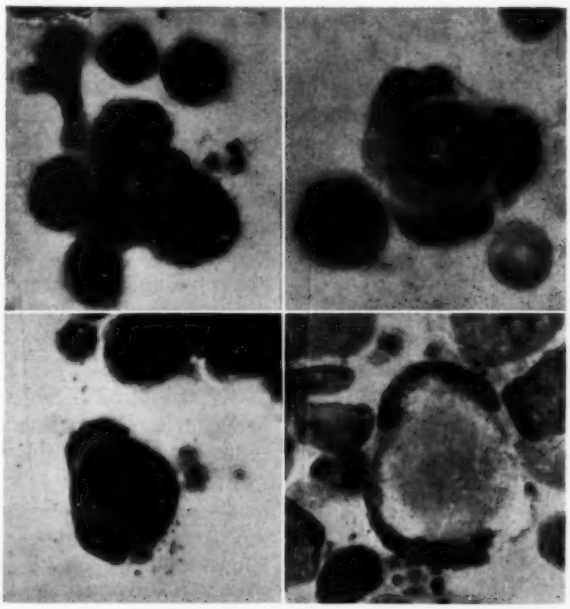

Fig. 2 (Case 2).—Bone marrow tissue. Polymorphonuclear leukocytes in various stages of engulfing extracellular nuclear mass. Lower right-hand photomicrograph shows typical "L.E." cell.

FOLLOW-UP REPORT ON CASES 1 AND 2

The patient in Case 1 was started on 200 mg. daily of cortisone as soon as the diagnosis of acute leukemia was established. Fever and sedimentation rate promptly returned to normal levels, and joint pains and tender areas disappeared. He was discharged to his home. Sixteen days later a repeat bone marrow aspiration showed no evidence of leukemia and the sedimentation rate was 1 mm. per hour.

He was again seen ten days later and this time all symptoms were returning and the tip of his spleen was palpable. However, no immature lymphocytes were demonstrable in a peripheral blood smear. Cortisone was increased to 300 mg. daily. His parents took him to another institution where the diagnosis of leukemia was confirmed and he was sent home to continue on cortisone.

Approximately five weeks after starting cortisone and while at home he suffered a sudden severe gastrointestinal hemorrhage from which he died.

The patient in Case 2 was also put on cortisone and discharged home. Although the immediate result was complete remission of symptoms, she died from her disease a month or so later at home.

Case 3. Hepatic Cirrhosis

DR. HILL.—Our next patient is a 39-month-old boy whom we have followed since early infancy. What seemed at first to be a simple problem has now turned into a rather difficult one. We are presenting him this morning because a decision has to be made as to what should be done next, and we shall welcome any suggestion any of you care to make. Dr. Pucci, will you tell us about this patient?

DR. MARY PUCCI (Resident).—R. S., aged 39 months, was first seen in this hospital when he was 6 weeks of age because of gradually increasing jaundice, first noticed when he was 3 weeks of age. His parents stated that he had also had symptoms of a cold for the past three weeks. Otherwise he was asymptomatic. At birth he weighed 8 pounds 8 ounces and at 6 weeks of age, 11 pounds 3 ounces. There was nothing unusual in the prenatal, natal, or postnatal periods. He was receiving an evaporated milk formula with added vitamins, and his intake was considered satisfactory.

The family history was negative. His mother was Rh positive, and her Wassermann test done during her pregnancy was negative. She had received no transfusions or injections of plasma, nor had she received any form of drug therapy during her pregnancy.

Physical examination showed an alert, active, deeply jaundiced infant. The liver edge was palpable 3 cm. below the costal margin and the spleen tip was palpable. There were no other abnormal findings except for the stools which were light in color, but only occasionally clay-colored. The urine was dark in color.

His red blood count was 3,730,000; hemoglobin, 11 grams; white blood count, 14,950 with 16 per cent segmented cells, 70 per cent lymphocytes, and 4 per cent monocytes. Urinalysis was negative on two occasions. The Kline test on both parents and the baby was negative. The baby was Rh positive. The initial icterus index was 54.1 units and the direct van den Bergh was 11.7 mg. per cent. The urine gave a positive test for bile and for bilirubin. Urobilinogen was absent in the first stool specimen examined, but on all subsequent examinations gave a positive test. Tests for bilirubin in the stool always gave a positive reaction but no quantitative estimations were carried out. Test of the red cells for fragility gave a normal result.

A number of liver function tests were done. Cephalin-flocculation was

3 plus in twenty-four and forty-eight hours. Thymol flocculation was ±1. Cholesterol was 263 mg. per cent, and cholesterol esters 174 mg. per cent. Alkaline phosphatase was 12.1 Bodansky units. Total protein was 5.44 grams of which albumin comprised 4.74 grams and globulin 1.70 grams. Prothrombin time was normal. The serum phosphorus was 5.5 mg. and urea nitrogen 18.6 mg. per cent. The heterophile antibody titer was 1:56.

During the next month of observation, the baby's condition remained practically unchanged. A trial of magnesium sulfate by duodenal catheter was made but with no improvement. It was finally agreed that the most likely diagnosis was incomplete obstruction of the biliary tract, and exploratory laparotomy was recommended. This was carried out when the baby was 3 months old. The liver was moderately enlarged. The upper portion of the common bile duct appeared to be distended, measuring 6 to 7 mm. in diameter. A fibrous veil covered and obstructed the distal portion of the common duct which was only 2 mm. in diameter. The fibrous tissue was divided, salt solution injected to demonstrate patency, and the wound closed. Unfortunately no biopsy was made of the liver.

Postoperatively the baby did well and it was thought the jaundice was clearing when he was discharged home twelve days later. The direct van den Bergh on this day was 3.0 mg. per cent.

He was seen from time to time in the outpatient department. Growth was excellent, but the liver remained enlarged and the sclerae were never free from some degree of icterus. On one of these occasions a needle biopsy of the liver was done. Little information was obtained, for microscopic examination of this particular specimen showed only increase in the fibrous stroma.

When he was 16 months of age he was again admitted to the hospital with the complaints that of late his appetite had become poor, he was irritable, and his gain in weight had slowed down. This time the liver was larger than ever, now being palpable some 5 cm. below the costal margin. Jaundice was still evident, and the parents said the stools had gradually become large and clay colored. X-rays of the wrists which were done for bone age revealed the somewhat surprising finding of typical rickets. The parents insisted that he had received his usual vitamin supplement regularly. Serum calcium was 7.8 mg. per cent and phosphorus was 2.94 mg. per cent. It was felt that this represented hepatic rickets and was the result of poor fat absorption. Alkaline phosphatase was 69.1 Bodansky units. A Bromsulphalein test gave a 30 per cent retention in forty-five minutes.

In addition to the teaspoon of polyvitamins (Mead's) which he had been receiving daily, 16 drops of Drisdol, sodium citrate, and citric acid were prescribed. When next seen five months later at the age of 21 months, he appeared greatly improved. Jaundice was not evident, his rickets had healed, and he was above average in both weight and height (34½ pounds, and 33½ inches). The liver edge was 4 cm. below the costal margin and the spleen was not palpable. Total serum bilirubin was 1.1 mg. per cent with 0.7 mg. direct and 0.4 mg. indirect. There was 40 per cent Bromsulphalein retention. Cholesterol was normal. Total

Fig. 3 (Case 3).—Roentgenogram of wrists. Showing rachitic changes at distal ends of ulna and radius. Hepatic rickets. Patient aged 16 months.

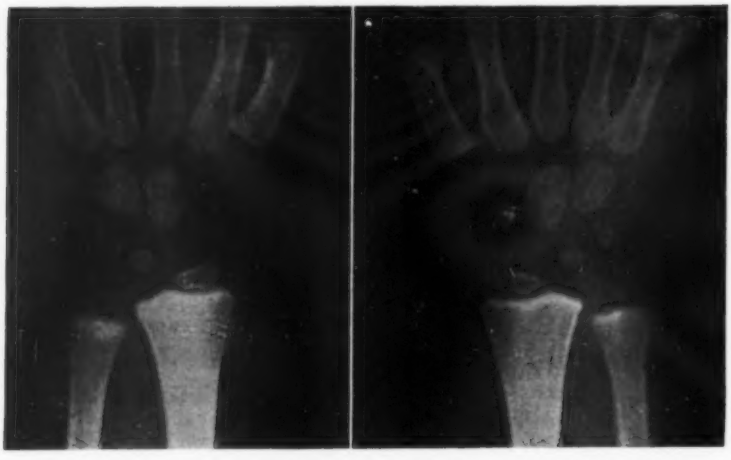

Fig. 4 (Case 3).—Five months later at age 21 months; rickets healed.

serum protein was 6.71 grams with 3.02 grams of albumin, and 3.69 grams of globulin. Albumin-globulin ratio was 0.80. Alkaline phosphatase was 14.9 Bodansky units and serum phosphorus had risen to 5.7 mg. per cent. Cephalin flocculation was 1 plus in twenty-four hours, and thymol flocculation was 4 plus.

He continued to do well until 36 months of age when he was again admitted to the hospital following an automobile accident. The liver was palpable 2 cm. below the costal margin. His spleen was now noted to be considerably enlarged, being palpable 5 cm. below the costal margin. The sclerae were again icteric. His red blood count was 3,370,000; hemoglobin, 9.3 grams; and white blood count 6,100. Total serum bilirubin was 5.9 mg. per cent with 3.5 mg. direct and 2.4 mg. indirect. There was 45 per cent Bromsulphalein retention, and cephalin flocculation was 4 plus. The child was asymptomatic and remained in the hospital only one day.

Now, at 39 months of age, he is in the hospital for a fourth time. Except for a poor appetite he was apparently well until ten days prior to admission when his abdomen began to enlarge rapidly and progressively. On physical examination, his abdomen was tense with what appeared to be fluid. The liver edge was 3 cm. and the spleen 7 cm. below the costal margin. Both were firm and nontender. His sclerae were icteric and generalized pallor to a severe degree was striking. The red blood count was 1,950,000; hemoglobin, 4.1 grams; and white blood count, 4,300. The platelets numbered 122,400, and there were 2.9 per cent reticulocytes. Smears of the peripheral blood revealed a hypochromic microcytic anemia. Erythrocyte fragility was normal. Coombs' test was negative. Prothrombin time was normal. There was no evidence of blood loss in stools or urine. The bone marrow was hyperplastic. The urine contained no bile, and the stools were of normal color. Liver function studies differed little from those which had previously been done. Esophageal varices were demonstrated by x-ray. Repeated blood transfusions have been given and the anemia is now much improved. Mercurial diuretics and a low salt diet have lessened the ascites. He was tapped once.

DR. HILL.—It is obvious that this patient has severe and progressive liver disease. He now presents many of the findings one sees in Banti's syndrome. Undoubtedly he has cirrhosis with portal obstruction, but as so often happens in cases of this type it is difficult to assign a clear-cut etiology. It seems doubtful that the obstruction to the common duct described by the surgeon at the original operation is alone responsible for the progressive liver damage. Possibly other obstructions to the biliary tract occurred higher up—even intrahepatic. Congenital cirrhosis is described but is not, in my thinking, a clearly defined clinical entity. Erythroblastosis and syphilis can be excluded. Toxic and infectious hepatitis are rare causes of liver disease in early infancy and there is little to cast suspicion on either of these conditions in our patient. However, it must be remembered that the baby did have a cold shortly after birth which might have given rise to a generalized sepsis. Unfortunately, no blood cultures were done. Against this possibility is the

excellent weight gain made in the first six weeks of life and the absence of symptoms of illness. Congenital hemolytic icterus can obviously be discarded. It would be my guess—and it can only be a guess—that a congenital abnormality of the biliary tract, probably intrahepatic, is responsible for the hepatic damage.

But whatever the etiology, our immediate problem is what should be done for him now. He has developed hypersplenism which is undoubtedly the cause of his severe anemia, and esophageal varices are present which sooner or later will rupture. We have had several consultants review this case and their advice has varied from "medical management," to portal-caval or spleno-renal shunt, to splenectomy alone. Most of us on the pediatric side favor, I think, a splenectomy.

Dr. Dorner from the surgical service is here and we might ask him his opinion.

DR. RALPH DORNER.—Personally, I believe splenectomy has the most to offer—at least as the initial step. Although his liver disease is severe and will probably ultimately be fatal, I feel that he should not be denied the temporary benefits of surgery. I doubt that he would tolerate an extensive procedure such as the spleno-renal shunt, even if such a procedure were technically possible. A splenectomy will decrease the portal blood flow, will lessen the possibility of esophageal hemorrhage, and will stop the rapid destruction of blood. Other procedures to consider are ligation of the hepatic artery, ligation of the vessels that supply the esophagus, and esophogastrectomy, but I think splenectomy will be the simplest and best tolerated procedure and give him the best chance for survival.

FOLLOW-UP REPORT

A few days after presentation of this patient at clinic a splenectomy was carried out. The organ was greatly enlarged, weighing 266 grams and measuring 15 × 9.5 × 6 cm. The microscopic picture was that of congestive splenomegaly.

The liver at operation was observed to be nodular and firm. Microscopic examination of a biopsied specimen was reported by the pathologist as follows: "The liver is composed of numerous tiny nodules of liver parenchymal cells separated from each other by an abundance of fibrous connective tissue stroma. The nodules vary in size but are somewhat larger than normal liver lobules; some of them are partially fused. Central veins are seldom encountered. The parenchymal cells are quite normal in appearance. The stroma is infiltrated by small numbers of lymphocytes; it is quite vascular; bile ducts are not very numerous. The picture in the liver is quite characteristic for diffuse nodular or Laennec's cirrhosis. It is simply the end stage of an old process, and the pathogenesis cannot be surmised on the basis of current sections. There is much more fibrosis than was seen in the needle biopsy specimen of June 8, 1949."

Splenectomy has certainly been beneficial in this patient. It has now been nearly six months since his operation (Oct. 8, 1951). His blood counts have remained up to normal levels without the aid of transfusions. His ascites has disappeared and his appetite has returned. Furthermore, he is growing at a normal rate and is no longer ill-natured.

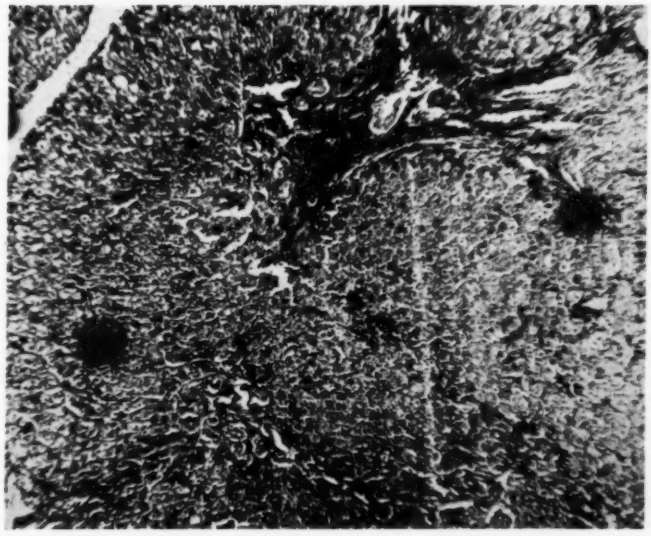

Fig. 5 (Case 3).—Vim-Silverman needle biopsy of liver. When patient was 11 months of age. Only slight increase in fibrous tissue stroma noted.

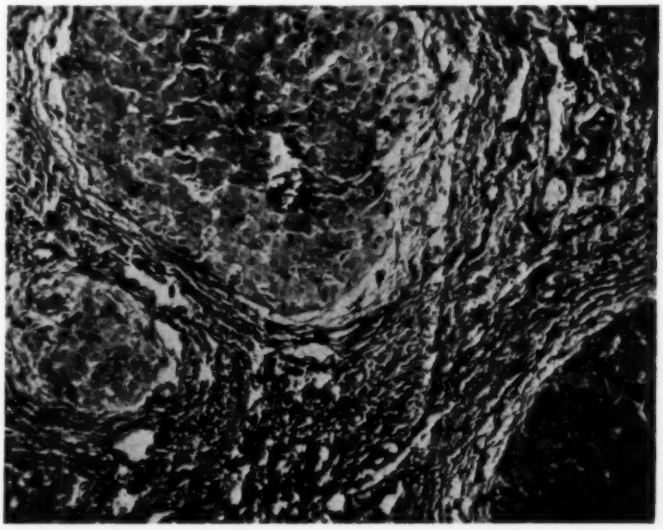

Fig. 6 (Case 3).—Photomicrograph of biopsy of liver obtained at time of splenectomy when patient was 39 months of age. Note nodules of liver parenchymal cells separated by abundant fibrous connective tissue stroma. Illustrates marked progress of liver damage in twenty-eight months.

An interesting side light in connection with this patient is that a male sibling born some two months ago also developed jaundice in the first week of life which became progressively more intense. The liver was large, the stools were acholic, and the urine dark. The evidence in this patient was quite conclusive for obstructive jaundice. An exploratory operation was done when

Fig. 7 (Case 3).—Photograph of patient with hepatic cirrhosis. Growth has been maintained at about average values.

the baby was 6 weeks of age. Again it was felt by the surgeon that an obstruction existed in the common duct. Adhesions were freed and two lymph nodes, one on either side of the common duct, were removed. Patency was demonstrated by injecting Lipiodol into the gall bladder and visualizing its presence in the intestine by x-ray.

Unfortunately the baby developed small bowel obstruction on the eighth postoperative day. This was relieved, but death occurred two days later from peritonitis. At autopsy, the hepatic duct was found to consist of a fibrous cord only, while the cystic and common ducts were patent.

From a casual perusal of the literature it would appear that the occurrence of multiple cases of congenital atresia of the bile ducts in a family is rather unusual. Sweet[2] was able to find reports of six families with two or more cases each and described one family with three such cases. Hopkins[3] reported three cases occurring in a family.

Case 4. Ureterocele, Duplication of the Kidney, and Hydro-ureter

DR. HILL.—Our final patient has a brief protocol. He has a congenital anomaly of the urinary tract which is somewhat different from those we are accustomed to seeing. Dr. Latchem is here from the urology service, and he will discuss the lesions. Dr. Nitchals would you tell us about this boy?

DR. JEANNE NITCHALS (Resident).—This is a 4-year-old white boy who was sent to this hospital because he had been unable to pass his urine for the preceding ten hours.

One week before admission he complained of vague abdominal pain, and he had lost his appetite. His mother noted redness around the urethral meatus. On the following day his urine was described as being of a "chalky" color. A local physician saw the boy and examined the urine. He commented on the presence of albumin and on its acidity. Penicillin, methyl-

ene blue, and forced fluids were prescribed.

On the day of admission the lower abdomen was distended and the boy was acutely uncomfortable. He stated that he had the urge to urinate but was unable to do so.

Two years ago he had had a similar brief episode of being unable to urinate. At that time a cystogram only had been done, and since it appeared to be normal, no further investigations were carried out. In the two-year interval there had been no further symptoms referable to the urinary tract.

On physical examination his temperature was 101° F., weight 36½ pounds, and height 39½ inches. The lower abdomen was distended and the bladder was palpable halfway to the umbilicus. An undescended testis was noted on the left. A systolic murmur, interpreted as functional, was heard at the base of the heart. His blood pressure was 110/74. The remainder of the examination was within normal limits.

A number or urinalyses were done. Specific gravity varied from 1.012 to 1.030. Albumin was found in small amounts in all specimens. Leukocytes were numerous, being recorded as 4 plus with clumps on several occasions. Erythrocytes varied from 1 plus to 3 plus. Urine culture yielded a few unidentified gram-negative rods and *E. coli*. These were sensitive to terramycin and to Chloromycetin. The Mantoux tuberculin test was negative. Blood urea nitrogen was 9.0 mg. per cent. Kline and Kahn tests were negative. Routine blood counts were normal. A cystogram followed by an intravenous pyelogram was done.

DR. HILL.—Dr. McMillan, would you comment on the films?

DR. JAMES MCMILLAN (Roentgenologist).—The first films on this boy were made in May, 1949, when a cystogram was performed and found to be normal. Another cystogram was done a few days ago. This time a large, lobulated, rounded, filling defect was seen within the bladder, displacing some of the medium.

An intravenous pyelogram was then done. In the flat film of the abdomen, prior to the injection of the medium, there is a rounded soft tissue density in the left mid-abdomen opposite the third lumbar segment. After the injection of the dye, you can see in this film (Fig. 8) that there was prompt function in both kidneys, and the right kidney is normal. In the left kidney we can account for only the lower and middle calices in the visible segment and notice how they are displaced laterally and rotated. There is also marked lateral displacement of the upper third of the left ureter by the previously noted soft tissue mass. Again the filling defect in the bladder can be seen and is clearer on this film than on the cystogram.

We reviewed the films with Dr. Latchem, and it was our opinion that the abnormality in the bladder was a large ureterocele. We felt it was associated with a poorly functioning and dilated upper segment of a reduplicated left kidney and that the soft tissue mass was a connecting hydroureter causing displacement laterally of the lower segment of the kidney and its ureter.

DR. HILL.—I am sure it is quite unnecessary for me to point out that in-

fections of the urinary tract are encountered much less frequently among boys than among girls. However, when boys do develop such infections, the chances of finding some significant abnormality about the urinary tract to explain the infections are much greater than girls. In private practice I suspect most of us treat at least one attack of pyelonephritis in the majority of our girl patients medically before resorting to urography. But such temporizing in boys is probably unwise. Dr. Latchem, would you tell us something about ureteroceles and their management.

Fig. 8 (Case 4).—Urogram showing ureterocele, and rotated and laterally displaced lower segment of left kidney and ureter. Duplicated upper segment with hydroureter not seen in this film.

DR. CHARLES LATCHEM (Urologist).—First, let me emphasize the statement made by Dr. Hill relative to urinary tract infections in boys. Urinary tract infections in the male without evidence of some sort of pathology are quite rare. This case is a good example of why all urinary tract infections, especially in the male, deserve complete urological investigation. Even though his complaint was retention and referable to the bladder neck alone, it can be seen from his urogram that he has more than one cause for pyuria.

We have discussed duplication of the kidney in this clinic before and therefore I shall limit my remarks to the development of the ureterocele and the part it has played in this case. This child represents the fourth or fifth case that I have seen in the past three years with complete duplication and ureterocele involving the upper segment. It is, therefore, not a rare lesion. Ureterocele has been reported frequently as causing urinary retention, and in female patients the sac has herniated out through the urethra. We have had one such case in this hospital.

In order for ureterocele to develop, there apparently must be two conditions present—first a small pinpoint ureteral orifice, and, second, a weakness of the ureteral wall behind the orifice. I have seen many small pinpoint orifices without ureterocele, but never a ureterocele with a normal or large orifice. It is felt by some that the weakness lies in Waldeyer's fascia which forms a part of the ureter. Ballooning out of this portion of the ureteral wall behind the stenotic orifice forms the characteristic sac.

The treatment of simple ureterocele varies somewhat with the size of the sac and the amount of damage that it has done. If the upper urinary tract is normal and the sac small, it may be left alone. If, however, the sac is causing symptoms or there is recurrent infection, then transurethral incision of the sac is usually adequate. Some prefer to open the bladder suprapubically and incise the entire sac, though I do not feel that in most instances this is necessary. Where the kidney is badly dilated or damaged above the ureterocele, nephrectomy is the treatment of choice with removal of the ureter and sac.

In this case the duplication of the left kidney was complete, the lower half being undamaged, and the upper half destroyed. A heminephrectomy and ureterectomy were done. In some cases it may be impossible to remove the vesical portion of the dilated ureter without jeopardizing the good ureter, since the two orifices are so close together. I felt that was the situation here, so the sac and a small portion of the distal ureter were left undisturbed. I have done this before without trouble. The urine in this patient has cleared and he is symptom free. If in the future there is a return of obstructive symptoms, it will be a simple matter to deal with the remaining sac in the bladder either transurethrally or suprapubically.

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Psychologic Aspects of Pediatrics

ADDICTION TO THE INHALATION OF GASOLINE FUMES IN A CHILD

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GASOLINE inhalation and intoxication is a well-known condition in industry. Workers in rubber and gasoline plants not infrequently suffer from inhalation of volatile hydrocarbons. The mental symptoms depend to a great extent upon the acuteness of onset and size of dosage. They probably vary also according to the personality pattern of the individual. Many instances of "naphtha jags" in rubber plant workers have been reported wherein the fumes of toxic hydrocarbon solvents are inhaled voluntarily to achieve a pleasurable feeling. The reaction is not always one of hilarity. The victim may show irritation and belligerence. Machle[1] reviews the literature in detail and discusses the symptomatology, the toxicology, and the pathological findings. The volatility of gasoline makes the effect a transient one, although repeated inhalation of a high concentration of fumes may cause damage to the central nervous system. It is difficult to ascertain to what extent lead poisoning occurs following inhalation of the fumes from gasoline treated with tetraethyl lead, but direct contact with this product is known to be a source of lead intoxication. Mention is also made of the fact that children are known to inhale gasoline occasionally out of curiosity. In 1900, Peters reported a 14-year-old feebleminded girl who became irritable and tense, and gave some evidence of having hallucinations following voluntary inhalation of benzene fumes. No detailed report of habituation or compulsive inhalation of gasoline has been found in the literature.

The present report deals with habituation to the inhalation of gasoline fumes in an 11-year-old boy who was studied and treated intensively from Aug. 10 to Sept. 30, 1948. Its purpose is threefold; namely, (1) to call attention to an unusual type of habituation in a child, (2) to point out how the patient used this behavior as a defense against anxiety, and (3) to demonstrate that Sodium Amytal interviews can be helpful in a child under certain conditions, not only in better understanding a complex problem, but also in shortening the total treatment time.

CASE REPORT

S.M., an 11-year-old boy, was first seen in the out-patient department of the University of Minnesota Hospitals with complaints of "nervousness," withdrawn behavior, daydreaming, inhalation of gasoline fumes, and depression. He was known to have inhaled gasoline fumes periodically since the age of 5 years. This practice had suddenly been much accentuated three weeks prior to admission. It was also reported that he smoked as much as a package of cigarettes daily.

Past Medical History and Physical Examination—The patient was the

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product of a normal full-term delivery. The neonatal course and the developmental history were normal. He had had the usual childhood diseases without complications. No injuries, operations, or accidents of any significance were noted.

He was a pale, slender, tense white boy who was in no acute distress but appeared quite anxious. Except for a moderate amount of conjunctival injection, the physical examination was negative as were repeated neurological examinations.

Family History—The patient was the second of four children. He has one sister, aged 12 years, and two brothers, aged 9 and 7 years, all apparently in good health.

The mother and father, both aged 31, were from stable backgrounds and were married approximately three years before the patient was born. At the time the boy was admitted to the hospital, the mother was obviously under emotional tension but denied feeling any need for psychiatric treatment.

The father was not seen. He was reported to be well but was said to have symptoms of duodenal ulcer. According to reliable information, the home life of this family had never been satisfactory. Continual marital discord, owing in part to the father's alcoholism and many absences from the family, had resulted in numerous parental separations and reconciliations during the patient's life. One week before the onset of the present illness, the parents were divorced. At about the same time the paternal grandfather, to whom the patient was devoted, died.

No history of familial diseases, mental illness or deficiency in the family was elicited.

Laboratory Examinations.—Hematological examinations, liver function tests, x-rays of the chest and long bones, and urinalysis were all negative, except for the urine protoporphyrins which were elevated.

The electroencephalogram was abnormal, there being 4 to 6 per second diffuse activity with paroxysmal 5 per second waves, indicating diffuse cortical damage and irritability. No focus of abnormality was noted.

On the Standford-Binet Intelligence Test, Form L, the patient showed a mental age of 9 years 9 months which gave him a calculated I.Q. of 89. Because he was tested under a stress situation, it was felt that the score should be interpreted in the light of his obvious anxiety. However, the psychologist suggested he would probably not test more than ten points higher if he were tested under more nearly normal conditions.

The Rorschach record suggested that he was depressed and anxious, although he was obviously trying desperately to maintain control of himself. No evidence of any break with reality was noted in the record and his ego strength was considered fair. Though there were signs suggestive of brain damage, they were not conclusive enough to justify this diagnosis.

Early during his hospital stay he appeared anxious and depressed. He tended to be withdrawn. He made no effort to establish relationships with wardmates or staff members. He bit his fingernails vigorously and cried frequently without provocation. He seemed suspicious of all adults and persistently denied the need of any help. He admitted "breathing gasoline" since the age of 5 years but was reluctant to discuss it further, except to admit that he liked the smell.

After several days in the hospital, he began to trust the therapist. He acknowledged that he felt depressed and was preoccupied with thoughts of death, and of homocide. Nevertheless, he denied any suicidal intent in his actions. He said these other feelings were stronger following his admission to the hospital.

Because of the lack of psychiatric facilities in the patient's distant home locality, and because of administrative difficulties which made it impossible to hospitalize him for more than a short period of time, it was decided to treat the patient with short-term, intensive psychotherapy, although the hazards were recognized. This exigency, more

than anything else, dictated the use of the Amytal interview technique, even though its limitations and hazards were recognized particularly as applied in the practice of child psychiatry.

After rapport was established by means of six preliminary interviews, a Sodium Amytal interview was given, using 3:75 gr. of Sodium Amytal intravenously. Under the influence of the Amytal, the patient was quickly regressed to the age of 5 years and began abreacting hallucinations which he had while under the influence of gasoline fumes. He recounted in the present tense the "little men who were horrid" who came out of the ground and who threatened him with death. Though it was apparent that he was anxious and fearful, he was able to describe the hallucinations in great detail. In addition he told of the extent and method of his gasoline breathing and of the marital discord in the family for which he felt responsible. After an interval of forty-five minutes the inquiry was terminated, amnesia was suggested, and the patient dropped off to sleep. It became apparent that the patient had meaningful hallucinations when breathing gasoline.

Following this interview, he was less tense. Concomitantly his ability to relate to the therapist and his wardmates improved. Daily interviews were held with him without Amytal. He was now able to talk about everyday occurrences and nonthreatening subjects. In addition he could talk more freely about his breathing gasoline. He volunteered, "I just have to breathe it." He seemed to appreciate the nature of his hallucinations. However, he could not tell about their meaning to him. Whenever a cautious suggestion was made to introduce some of the material elicited under Amytal, he became depressed, anxious, and uncommunicative.

One week after the first interview was held under the influence of Sodium Amytal, a second intervenous injection of the drug was made. The following information was elicited by direct questioning on this occasion. The gasoline inhalations had apparently begun quite accidentally when the boy was 5 years of age, primarily out of his curiosity. Initially he breathed the gasoline fumes only occasionally. Each time, however, he had a pleasant hallucination of friendly, pleasant, gnome-like men who were fond of him and spoke kindly to him. At this time parental discord was intense. The patient felt that his father was abusive and severe with him. "Father heckled me and gave my mother and me heck at everything we did." Because of this, he began to plot with the men of his hallucinations to remove the father. He said, "I want to make my father go away, so I can go off someplace with mom and we can make a living together and be happy together on a farm." His hallucinations promised to help him if he would never "call" again. Quite by coincidence the father left on a three weeks' trip about this time. The patient interpreted this as the fulfillment of his wish and believed the hallucinations helped him to do away with his father. However, the father returned after a short absence from home.

The patient continued to inhale gasoline, despite great pressure to desist. The character of the hallucinations changed. Instead of being friendly as before, they became threatening and hostile. He related how the little men began to say they were going to kill him because he had double-crossed them by repeatedly calling them up from the ground. Furthermore, they were now armed with guns and knives. From this time on the patient increased the inhalations of gasoline. He often breathed fumes to the point of becoming unconscious, repeating this performance several times a day.

This behavior continued until the family moved to town. Here the intensity of the conflict apparently lessened; also, gasoline was not so easily available as on the farm. It was at this time that the patient became tense, anxious, and depressed. His social adjustment in town was border line. Gasoline inhalation from automobile tanks con-

tinued sporadically until the onset of the present episode three weeks prior to hospital admission. The two upsetting circumstances already referred to then developed. The poor marital adjustment of the parents resulted in divorce, and the paternal grandfather died. The boy was then placed on a farm where the inhalation of gasoline fumes was resumed with increased frequency. In independent interviews the mother corroborated the essential features of this story. However, she was completely unaware of the hallucinations or of the meaning of his behavior.

For some time the patient continued to have amnesia for the material gathered under the influence of Amytal, although this had been suggested following each interview of the kind. With patience and gentle encouragement on the part of the therapist, confidence in him continued to develop. The material obtained under Amytal was gradually introduced to the patient and was accepted by him. He began to understand the meaning of his behavior and the cause of his troubles. He then found it possible to talk about his difficulties and his feelings of guilt without crying, biting his nails, or withdrawing. He became more relaxed and sociable on the ward and enjoyed many of the group activities as he formed new friendships. His appetite improved and he gained 8 pounds. Gradually his anxiety lessened and his depression disappeared.

Prior to his discharge from the hospital several suggestions were offered to the mother regarding environmental changes. As a result he was placed with his maternal grandparents whom he liked. This plan also made it possible for him to attend a small school where his teacher took a personal interest in him.

When seen at the clinic ten weeks after discharge, he had gained 14 pounds and was making a good social adjustment at school and at home. He had breathed no more gasoline and denied any desire to do so. Some difficulty with his school work was reported. This was thought to be related to his low normal intellectual capacity. When retested, his I.Q. was the same as before. It was felt that some damage to the central nervous system had occurred as a result of the gasoline inhalation because the electroencephalogram remained abnormal. However, re-examination by means of the Rorschach test showed a lessening of anxiety and better handling of reality.

DISCUSSION

The use of Amytal in this case was predicated on several circumstances. The patient's symptomatic behavior was such as to endanger his physical well-being irreversibly. He lived in an area devoid of psychiatric facilities and hospitalization was possible only for a limited period of time. So, temporizing or slow uncovering therapy was not possible.

Use of Amytal interview in child psychiatry is not to be undertaken lightly and the indications for its use are definite. The method has been tried in a few selected cases by others during the past several years. As with this case, it has been found helpful when judiciously used. On the basis of our limited experience we have drawn a few tentative conclusions for our own future guidance in dealing with special problems for which the procedure might be considered. At the present time we believe that its use should be restricted to those cases, like the present, in which the patient is likely to suffer irreversible damage from his behavior and in situations where time and facilities for more conventional treatment methods are not available in the local community.

It is our impression that the "anxiety" material introduced into consciousness should be presented by degrees over as long a period of time as possible. The use of this technique with

children is primarily to gain information rather than to induce real abreaction which in our opinion may be too violent for a neurotic child to handle successfully. For this reason, Amytal, rather than Pentothal, is the drug of choice. Amnesia is suggested rather than encouraging the patient to talk the material up to consciousness.

It is most important that the closest rapport possible between patient and therapist be established before attempting use of the procedure. It should be explained thoroughly in order that the cooperation of the patient may be obtained. One must be continually aware of the fact that a child may easily misinterpret one's actions as a hostile attack. The usual safety precautions regarding use of the drug are perhaps more important with children than with adults. This method should be limited strictly to hospitalized patients who can be closely observed during recovery. With the patient in the hospital, interviews can be held daily or even oftener if necessary. The reasons for using such a procedure must be thoroughly explained to parents and written permission should be obtained.

In the present case the use of Sodium Amytal interviews enabled us to secure significant data concerning the patient's life experiences, and his reactions and feelings toward them more quickly than would have been possible by other methods. In the light of the help thus obtained, the patient's compulsive need to breathe gasoline as a defense against overwhelming anxiety became clear. Likewise, the reason for the exacerbations which finally resulted in his referral to us became more understandable. This information permitted attack upon the problems with greater confidence. With due regard for the patient's feelings and the need for careful interpretation, this repressed material was gradually introduced into the treatment sessions. The marked change in his attitude and disposition indicated that he had sufficient strength to handle his difficulties in the therapeutic situation without too much difficulty. The final result was highly satisfactory. It is doubtful if the management of the problem could have been as effective by the use of ordinary methods.

SUMMARY AND CONCLUSIONS

A typical case of addiction to the inhalation of gasoline fumes in an 11-year-old boy is reported. Suggestive evidence of brain damage resulting from prolonged and excessive inhalation of the hydrocarbon fumes is presented.

The use of Sodium Amytal interviews was found to be highly effective as an aid in securing crucial data concerning the psychogenic factors involved in the etiology.

Psychotherapy based upon such findings was highly successful in ridding the patient of his addiction while resolving his underlying anxiety state.

Special indications for use of the drug-interview technique are cited. Precautions against its abuse should be borne in mind.

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Comments on Current Literature

EFFECT OF CORTISONE ON EXPERIMENTAL POLIOMYELITIS INFECTION

VARIATION in host response to infectious agents has been the subject of much speculation and has prompted extensive experimental investigation. Since there are so many factors involved in the host-parasite relationship, evaluation of data has often failed to yield clear-cut conclusions. The recent publication of Gregory Shwartzman and Alice Fisher,[1] however, dealing with the enhancement of poliomyelitis infection by means of cortisone, presents convincing evidence that the host-parasite relationship is altered significantly by this hormone. The clinical observation that pregnancy is associated with both hyperfunction of the adrenal cortex and an increased susceptibility to poliomyelitis prompted these authors to undertake this fundamental study.

The Syrian hamster was selected as the laboratory animal because this particular species is known to be partially refractory to infection with the virus of poliomyelitis. This choice of experimental host was a well-calculated one since the results proved to be definite, to be reproducible, and capable of verification in statistically significant numbers of animals. The authors demonstrated that cortisone enhanced experimental poliomyelitis in the Syrian hamster in "shortening of incubation period, increased severity of symptoms, marked reduction in mean survival time, and an increase in the mortality rate." It was also shown that the more cortisone used, the smaller the amount of virus needed to produce severe infection, and the less cortisone used, the greater the inoculum of virus needed to produce a comparable effect. Cortisone was found to enhance the virus effect not only by facilitating invasion of the viral agent, but also by increasing significantly the concentration of virus in brain tissue of the cortisone-treated hamsters as compared with untreated hamsters. It was of note that one strain of hamster studied failed to react to the cortisone effect. This part of the experiment suggested that there may be an inherent difference of host response even in a single species of animal.

ACTH, desoxycorticosterone acetate, progesterone, and diethylstilbesterol were studied also, but failed to enhance the viral infection in the hamster.

Further studies with monkeys (Sabin[2]) demonstrated that cortisone has an enhancing effect on poliomyelitis infection in primates as well as in rodents. Using a Lansing strain of virus of low virulence, it was shown that cortisone is able to convert nonparalytic and mildly paralytic infection in monkeys to severe prostrating paralysis.

On the basis of the foregoing studies, it appears evident that cortisone can alter the host-virus relationship and does exert a profound effect on the clinical manifestations of this virus disease. Whether a similar hormonal effect is important in naturally-occurring poliomyelitis infections in man is problematical and must await further study. However, as the authors point out, it may be of significance that temporary disturbance in adrenocortical function with

hypersecretion of glucocorticosteroids may be a factor in the increased susceptibility of human subjects under stressful situations, e.g., excessive physical fatigue, surgical procedures, trauma, pregnancy, and prophylactic vaccination.

These studies of poliomyelitis infection in the experimental animal, and references to similar observations of hormonal effect on other viral infections suggest that endocrine balance may indeed play a significant part in determining the nature of clinical manifestations of virus infections in man as well as in experimental animals.

RUSSELL J. BLATTNER.

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Erratum

In the article by Dr. Nancy Bayley and Mr. Samuel R. Pinneau entitled "Tables for Predicting Adult Height From Skeletal Age: Revised for Use With the Greulich-Pyle Hand Standards," page 423 of the April issue of the JOURNAL, the last six columns of figures in Table IID were not aligned properly. Following is the correct table:

TABLE IID. ACCELERATED BOYS. PERCENTAGES AND ESTIMATED MATURE HEIGHTS FOR BOYS WITH SKELETAL AGES ONE YEAR OR MORE ADVANCED OVER THEIR CHRONOLOGICAL AGES:

SKELETAL AGES 12 THROUGH 17 YEARS

Skeletal Age	12-0	12-3	12-6	12-9	13-0	13-3	13-6	13-9	14-0	14-3	14-6	14-9	15-0	15-3	15-6	15-9	16-0	16-3	16-6	16-9	17-0
% of Mature Height	80.9	81.8	82.8	83.9	85.0	86.3	87.5	89.0	90.5	91.8	93.0	94.3	95.8	96.7	97.1	97.6	98.0	98.3	98.5	98.8	99.0
Ht. (inches)																					
49	60.6																				
50	61.8	61.1	60.4																		
51	63.0	62.3	61.6	60.8	60.0																
52	64.3	63.6	62.8	62.0	61.2	60.3															
53	65.5	64.8	64.0	63.2	62.4	61.4	60.6														
54	66.7	66.0	65.2	64.4	63.5	62.6	61.7	60.7													
55	68.0	67.2	66.4	65.6	64.7	63.7	62.9	61.8	60.8												
56	69.2	68.5	67.6	66.7	65.9	64.9	64.0	62.9	61.9	61.0	60.2										
57	70.5	69.7	68.8	67.9	67.1	66.0	65.1	64.0	63.0	62.1	61.3	60.4									
58	71.7	70.9	70.0	69.1	68.2	67.2	66.3	65.2	64.1	63.2	62.4	61.5	60.5	60.0							
59	72.9	72.1	71.3	70.3	69.4	68.4	67.4	66.3	65.2	64.3	63.4	62.6	61.6	61.0	60.8	60.5	60.2	60.0			
60	74.2	73.4	72.5	71.5	70.6	69.5	68.6	67.4	66.3	65.4	64.5	63.6	62.6	62.0	61.8	61.5	61.2	61.0	60.9	60.7	60.6
61	75.4	74.6	73.7	72.7	71.8	70.7	69.7	68.5	67.4	66.4	65.6	64.7	63.7	63.1	62.8	62.5	62.2	62.1	61.9	61.7	61.6
62	76.6	75.8	74.9	73.9	72.9	71.8	70.9	69.7	68.5	67.5	66.7	65.7	64.7	64.1	63.9	63.5	63.3	63.1	62.9	62.8	62.6
63	77.9	77.0	76.1	75.1	74.1	73.0	72.0	70.8	69.6	68.6	67.7	66.8	65.8	65.1	64.9	64.5	64.3	64.1	64.0	63.8	63.6
64	79.1	78.2	77.3	76.3	75.3	74.2	73.1	71.9	70.7	69.7	68.8	67.9	66.8	66.2	65.9	65.6	65.3	65.1	65.0	64.8	64.6
65	80.3	79.5	78.5	77.5	76.5	75.3	74.3	73.0	71.8	70.8	69.9	68.9	67.8	67.2	66.9	66.6	66.3	66.1	66.0	65.8	65.7
66		80.7	79.7	78.7	77.6	76.5	75.4	74.2	72.9	71.9	71.0	70.0	68.9	68.3	68.0	67.6	67.3	67.1	67.0	66.8	66.7
67			80.9	79.9	78.8	77.6	76.6	75.3	74.0	73.0	72.0	71.1	69.9	69.3	69.0	68.6	68.4	68.2	68.0	67.8	67.7
68					80.0	78.8	77.7	76.4	75.1	74.1	73.1	72.1	71.0	70.3	70.0	69.7	69.4	69.2	69.0	68.8	68.7
69						80.0	78.9	77.5	76.2	75.2	74.2	73.2	72.0	71.4	71.1	70.7	70.4	70.2	70.0	69.8	69.7
70							80.0	78.7	77.3	76.3	75.3	74.2	73.1	72.4	72.1	71.7	71.4	71.2	71.1	70.8	70.7
71								79.8	78.5	77.3	76.3	75.3	74.1	73.4	73.1	72.7	72.4	72.2	72.1	71.9	71.7
72								80.9	79.6	78.4	77.4	76.4	75.2	74.5	74.2	73.8	73.5	73.2	73.1	72.9	72.7
73									80.7	79.5	78.5	77.4	76.2	75.5	75.2	74.8	74.5	74.3	74.1	73.9	73.7
74										80.6	79.6	78.5	77.2	76.5	76.2	75.8	75.5	75.3	75.1	74.9	74.7
75											80.6	79.5	78.3	77.6	77.2	76.8	76.5	76.3	76.1	75.9	75.8
76												80.6	79.3	78.6	78.3	77.9	77.6	77.3	77.2	76.9	76.8
77													80.4	79.6	79.3	78.9	78.6	78.3	78.2	77.9	77.8
78														80.7	80.3	79.9	79.6	79.3	79.2	78.9	78.8

News and Notes

The following were certified by the **American Board of Pediatrics,** at the examination at San Francisco, Calif., June 27, 28, and 29, 1952.

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Dr. Hans Hartenstein, 1st Lt. (MC) 0192-1164, Ryukyus Army Hosp., 8114th A. U., APO 719, c/o PM, San Francisco, Calif.
Dr. Robert R. Haumeder, 273 Douglas Lane, Walnut Creek, Calif.
Dr. Oliver Morton Henderson, 50 Selfridge St., Vallejo, Calif.
Dr. Herbert Herzon, 515 School St., Pittsburg, Calif.
Dr. Abram Hodes, 1963 Pershing St., San Bernardino, Calif.
Dr. Maurice Harry Jennison, Lt.(jg) MC USNR, 902 D Bougainville, Oceanside, Calif.
Dr. Adrian Richard Jensen, Peacy Manor Apts., Rt. #1, Waukegan, Ill.
Dr. Harry Kaufman, 3959 Laurel Canyon, Studio City, Calif.
Dr. Vincent Charles Kelley, Dept. of Pediatrics, University of Utah, Salt Lake City, Utah.
Dr. C. Henry Kempe, Dept. of Pediatrics, University of California Hospital, San Francisco, Calif.
Dr. Walter James Kennedy, Jr., 5102 Bitter Root Way, Rt. #3, Yakima, Wash.
Dr. Clyde August Kirchhoff, 72 Eugenia Dr., Ventura, Calif.
Dr. Irving Neil Klitsner, 130 N. La Cienega, Los Angeles, Calif.
Dr. Geza Joseph Krempels, 529 E. 10th St., Long Beach, Calif.
Dr. Tempe Chester Lambert, 777 Bryant St., Palo Alto, Calif.
Dr. Harry James Lawler, 1131 N. 29th St., Billings, Mont.
Dr. Glenn E. Lembert, 1104½ Main Street, Vancouver, Wash.
Dr. Bertha Marion Levy, 1200 N. Walker, Oklahoma City 3, Okla.
Dr. William A. McMain, Jr., 60 South 4th E., Suite No. 26, Salt Lake City 2, Utah.
Dr. Lewis Richard Miller, Peninsula Clinic, 500 Arguello St., Redwood City, Calif.
Dr. John Roy Mitchell, Box "O," Ancon, Panama Canal Zone.
Dr. Theodore Ashton Montgomery, 3115 W. 76th St., Los Angeles 43, Calif.
Dr. Edward Mitchell Moss, Lt.(MC) USNR, 4152 Randolph St., San Diego, Calif.
Dr. Mary Mulloy, Children's Hospital, 4614 Sunset Blvd., Los Angeles 27, Calif.
Dr. Thomas Lothian Nelson, P.O. Box 1488, Eldridge, Calif.
Dr. Robert Hall Palmer, 23 Baldwin Ave., San Mateo, Calif.
Dr. Alexander Cranston Peat, Major, 39th Med. Group, APO 942, c/o PM, Seattle, Wash.

Dr. Hugh J. Plumb, Jr., 420 Jasmine, Corona Del Mar, Calif.
Dr. Venustiano Pulido, 3959 Laurel Canyon Blvd., Studio City, Calif.
Dr. Ronald Reuben, 6317 Wilshire Blvd., Los Angeles 48, Calif.
Dr. Don Brooks Rice, 204 Bcivin Bldg., 110 N. 6th St., Klamath Falls, Ore.
Dr. William Taylor Robinson, Woodland Clinic, Woodland, Calif.
Dr. William Boulware Schafer, 3907 Ocean View Blvd., Montrose, Calif.
Dr. Marvyn Sherman Schwartz, 1590 North Van Neso, Fresno, Calif.
Dr. Harry Daniel Shaffer, 805 Prairie Rd., Colorado Springs, Colo.
Dr. Robin Smith, 104 N. Commercial St., Neenah, Wis.
Dr. Joseph A. Stool, 3718 Travis, Houston, Texas.
Dr. Phillip Sturgeon, 4614 Sunset Blvd., Los Angeles, Calif.
Dr. Donald Arthur Sutherland, 11326 Second Ave., N. W., Seattle 77, Wash.
Dr. Wataru Walter Sutow, Capt. MC 0-19-21810, Atomic Bomb Casualty Commission, APO 182, c/o PM, San Francisco, Calif.
Dr. Warren Roswell Tepper, 1322 Penn St., Salt Lake City, Utah.
Dr. Lloyd Allen Thomas, Capt., Qtrs. T 315 A, Camp Stoneman, Calif.
Dr. Peter S. Tolins, 328 Maple St., San Diego 3, Calif.
Dr. James Louis Tucker, 120 Northgate Plaza, Seattle, Wash.
Dr. Robert Glenn Tyson, Permanente Hospital, Vallejo, Calif.
Dr. Daniel John Vracin, 10727 S. Paramount Blvd., Downey, Calif.
Dr. John A. Whittinghill, 2814 Ninth Ave., North, Billings, Mont.
Dr. John W. Wood, Atomic Bomb Casualty Commission, APO 182, c/o PM, San Francisco, Calif.
Dr. Herbert M. Woodcock, 1568 Paulsen Bldg., Spokane, Wash.

The following oral examinations have been scheduled:

Chicago, Ill., Oct. 24, 25, and 26, 1952.
Boston, Mass., Dec. 5, 6, and 7, 1952.

Dr. Elmer W. Barron, professor of pediatrics at the Tufts College Medical School from 1929 to 1942, died in Boston, Jan. 20, 1952, aged 75.

Dr. Andrew J. Thornton, of San Diego, Calif., died March 3, 1952.

Dr. Jean Crump has been appointed professor of pediatrics and chairman of the department at the Woman's Medical College in Philadelphia.

The 1953 meeting of the **American Pediatric Society** will be held at the Hotel Traymore in Atlantic City on May 6, 7, and 8. The meeting of the Society for Pediatric Research will be held on May 4, 5, and 6.

Eight fellowships for pediatric residents have been made available through the **American Academy of Pediatrics** by Mr. D. Mead Johnson and Mead Johnson and Company. The awards are $1,000 each for a period of one year and will be made annually, beginning Jan. 1, 1953. Criteria for the awards are as follows: (1) a letter from the Chief of Service indicating that the proposed individual has completed, or will have completed by Jan. 1, 1953, one year of pediatric training credited by the American Board of Pediatrics; that the resident has performed his work ably; and that there is real need for financial assistance; (2) a letter from the resident requesting the fellowship stating that he intends to enter pediatric private practice at the conclusion of his second year of training. The awards will be limited to seven to the United States and one to Canada. Research interests and accomplishments and desire to enter academic pediatrics are not criteria for the awards. Members of the Committee on Residency Fellowships of the Academy are: Dr. James Hughes, Chairman, Dr. Henry Poncher and Dr. Robert Lawson. Those interested may correspond with Dr. James Hughes, Le Bonheur Children's Hospital, Memphis 5, Tenn. The deadline for receipt of applications will be Oct. 1, 1952.

The pediatric staff of the **Cook County Hospital** announces that the Fourth Annual Morris Lamm Blatt Memorial Fund lecture will be given Tuesday, Oct. 7, 1952, in conjunction with the Julian Levinson Research Foundation. Dr. Herman Yannet, associate clinical professor of the department of pediatrics of Yale University and medical director of the Southbury Training School, Southbury, Conn., will speak on "Medical Aspects of Mental Deficiency." The lecture will be presented at 8:30 P.M. in the Medical Amphitheatre of the Cook County Hospital.

Editor's Column

PROPHYLAXIS OF OPHTHALMIA NEONATORUM

IN 1883 Carl Credé announced the success of his method for the prophylaxis of gonorrheal ophthalmia. He asserted that this method was practically 100 per cent effective and that it was to an equal degree harmless.

Credé insisted that his method be followed explicitly:

"Immediately after the cord is tied . . . the eyes are externally cleansed using clean cotton and ordinary clean water. Then the eyelids are held open by the fingers of an assistant and a single drop of 2% silver nitrate solution, hanging from a glass rod, is approximated to the cornea and allowed to drop in. All other care to the eye is omitted and the silver nitrate is not repeated if, during the next 24 to 36 hours, a small amount of redness or exudate appears."

It is not surprising that the value of this method was not seriously challenged during the many years when ophthalmia neonatorum was a leading cause of blindness, when there was no really effective treatment and no alternative preventive measure, and that both custom and statute caused Credé prophylaxis to be mandatory.

Few physicians of experience would subscribe to the view that protection is complete nor does it seem at all plausible that the single application of any antiseptic agent could be. Irritating effects are apparently a matter of variable experience. Merely to separate the eyelids may involve considerable trauma. Chemical irritation in the completely tearless eye of many newborn infants may be quite severe. At times, and in certain hospitals, purulent chemical conjunctivitis almost constantly occurs, perhaps because of the very zeal with which the method is employed. This reaction usually clears in a few days during which pus fairly rolls from the babies' eyes; meanwhile it may mask possible infection, and inflammation of the nasolacrimal duct may subsequently persist. Sometimes the silver nitrate is promptly washed out with salt solution which terminates the irritant effect but equally terminates the antiseptic action.

During the last decade the therapy of newborn ophthalmia has become so effective as to make any method of prophylaxis unacceptable unless it be completely protective and entirely harmless.

Credé's published data record an astounding incidence of ophthalmia:

YEAR	NO. OF BIRTHS	NO. EYE INFECTIONS	PER CENT
No prophylaxis			
1874	323	45	13.6
1875	287	37	12.9
1876	367	29	9.1
1877	360	30	8.3
1878	353	35	9.8
1879	389	36	9.2
1880 (until May)	187	14	7.6
	2,266	226	10.0
With $AgNO_3$ prophylaxis			
1880	211	1	0.5
1881	400	1	0.25
1882	418	2	0.5
1883 (3 months)	131	0	0.0

Notwithstanding the impressive contrast in this treated and untreated series, which would seem to sustain Credé's estimate of the value of his method, where in the United States today may a comparable incidence be expected? Is it conceivable that, whatever its value, silver nitrate prophylaxis is everywhere employed by physicians, nurses, and midwives with such necessarily meticulous care as to be responsible for our present incidence as contrasted with that in Credé's untreated series? Credé was most insistent that this procedure would avail only if carried out exactly as he directed and stated that those who had introduced minor variations had results which were very poor.

In California in 1950 there were 242,662 births and only ten cases of ophthalmia neonatorum which probably compares with the experience throughout the nation. It is altogether likely that such a series includes a sufficient number of inadvertent controls in which Credé's method was not exactly followed to make the low incidence not ascribable to successful prophylaxis.

There have been numerous studies which have attempted to determine the relative value of silver nitrate and of penicillin instillations but these studies have shown such a low over-all incidence of infection as to make comparison inadequate.

It remained for Leff[1] to employ only simple flushing of the eye with sterile water—perhaps this was the really significant portion of the original Credé method. No infections occurred in 4,500 deliveries.

Lehrfeld[2] and others have repeatedly proposed that nothing should be done prophylactically to the eyes of the newborn infant, thus eliminating both mechanical and chemical trauma. Emphasis would then properly be placed upon the treatment of the infected mother and the early detection and intensive treatment of the occasionally infected baby. Today this treatment should be almost unfailingly successful.

The question arises as to whether Credé prophylaxis should cease to be a matter of statute and of medical subservience to tradition. Today the incidence of gonorrheal ophthalmia is extremely low in most states. In 1950 its incidence was 0.004 per cent in California, as contrasted with approximately 10 per cent when silver nitrate was introduced by Credé in 1880. In 1951 80 per cent of the deliveries in the United States were in the hospital where the infants are under close supervision during the incubation period for the disease, and adequate therapy is available for treatment in the rare instances where ophthalmia occurs. Is there any reason to continue by statute and custom an anachronistic preventive method which in itself is not without harmful effects?

E. B. S.

REFERENCES

1. Leff, Morris: West. J. Surg. 59: 176, 1951.
2. Lehrfeld, Louis: J. A. M. A. 135: 306, 1947.

PRENATAL SEX DETERMINATION

THE question of whether it will be a boy or a girl is always of interest to parents of a child on its way. While the guess as to a male is approximately a 53:50 chance, prenatal determination has been a matter for the astrologer or other soothsayer, as there

has never been a scientific method of prediction.

In a recent preliminary report in Science,* Rapp and Richardson of Chicago present an observation which, if verified by other workers, would permit the prenatal determination of sex with a fairly high degree of accuracy. Richardson,† in 1951, reported an early test for pregnancy based on the presence of free estrone in contrast to bound or modified estrone in the urine. The study has been carried on to include other fluids as the blood, saliva, and tears. Free estrone was noted in the saliva in only some women by the sixth to seventh month of pregnancy. In nearly every case where an association of its presence in the urine and saliva occurred, a male child was born, and when the association was absent, a female. Their figures are as follows:

	Association Positive	*Association Negative*
Males	218	3
Females	7	148

Their data have not been published in full, and the preliminary report was for the purpose of allowing early verification of the observation by others.

Granted that the test proves to be a method for prenatal sex determination with a high degree of accuracy, the question arises as to its usefulness. The sex of the unborn child cannot be changed, and the sex of the infant must be accepted as such by the parents. Except to satisfy curiosity, predetermination can have but little usefulness. On the other hand, it is quite conceivable that such knowledge might do considerable harm in some instances. The parents most interested in the sex of the unborn child are usually those who have had two or three children of the same sex, and are trying again for a child of the other sex, perhaps that the family name might be carried on, or perhaps to fulfill an intense desire for a girl in the family. Although such parents usually try to conceal it, there is often an intense desire for a child of a certain sex. The disappointment when another boy or another girl arrives usually soon disappears, and the new baby is accepted and receives the same love and affection as the previous ones. Would this be the case if the mother of several children of the same sex becomes pregnant again in the hope of having a child of the opposite sex, and learns that her hopes and desires are in vain when she still has three more months of pregnancy? It is quite conceivable that during this time of waiting she might develop a rejecting attitude to the unborn child which will be deep-seated and persist, and the disappointment will not be short-lived as it usually is when she first learns the sex of the infant after birth.

*Rapp, G. W., and Richardson, G. C.: Science 115: 265, 1952.

†Richardson, G. C.: Am. J. Obst. & Gynec. 61: 1317, 1951.